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Surface Measurement Systems AAPS Posters 1999-2021





2021

1. Studying Moisture Induced Transformations and Degradation of Pharmaceutical Ingredients Using Raman Spectroscopy Combined with Dynamic Vapor Sorption

Daniel J. Burnett, David Bernick, Vikram Karde, Jerry Y.Y. Heng, and Frank Thielmann

For many materials, chemical and physical transitions can be influenced by the amount of water vapor surrounding the sample. Water vapor can associate with a solid in many ways, such as adsorb only on the surface, absorb deep into the bulk structure, chemisorb to the surface, act as a plasticizing agent forcing a glass transition and potentially inducing spontaneous recrystallization, or chemically react with the solid. In addition, the influence of moisture and heat on the stability of a solid drug is of fundamental importance in the physical, chemical, and biological stability of pharmaceutical materials. In this study, the combination of automated water sorption technology and Raman spectroscopy were used to detect, monitor, and measure humidity induced chemical degradation or other transformations of common pharmaceutical ingredients.



2020

2. Temperature and humidity degradation of API's studied by dynamic vapor sorption and in-situ Raman spectroscopy

Daniel Burnett, David Bernick, Frank Thielmann, Jerry YY Heng, Vikram Karde, Ian Rothsbottom

For many materials, chemical and physical transitions can be influenced by the amount of water vapor surrounding the sample. In addition, the influence of moisture and heat on the stability of a solid drug is of fundamental importance in the physical, chemical, and biological stability of pharmaceutical materials. As a result, stability studies of new drug moiety are mandatory before filing registration. In addition, forced degradation methodologies of pharmaceutical ingredients can quickly detect if degradants are likely to be generated in a drug substance and help to develop stability indicating methods. In this study, the combination of automated water sorption technology and Raman spectroscopy were used to detect, monitor, and measure humidity-induced chemical degradation of common active pharmaceutical ingredients (API's).

3. Examining surface interactions of glycine and its oligomers from experimental and molecular modelling approaches

Vikram Karde, Ian Rosbottom, Mingxia Guo, Jerry Heng, Daniel Burnett, Frank Thielmann

Glycine is the simplest of naturally occurring amino acids and has an immense physiological significance as a building block of biomolecules like peptides, proteins and precursor for diverse biometabolites.



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Understanding the surface interactions of these molecules becomes important as these could influence their biological reactivity, binding interactions in different bioprocesses and functionality of biomolecules. The objective is to examine glycine and its oligomers for determining the influence of progressively increasing chain length on the surface properties and investigating their water interaction tendencies.

4. Permeation and absorption of ethanol/water mixture through ethylcellulose film

Jin Zhao, Daniel Burnett, Armando R. Garcia, Jason Folkenroth

Ethylcellulose (EC) has been widely used as water-insoluble and rate controlling polymer for the coating of oral solid dosage forms, and as an excipient for amorphous solid dispersions of the active, as well as for buccal and transdermal drug delivery systems. The interaction of alcohol/water mixture with EC films will ultimately impact the drug delivery of the dosage form and thus the therapeutic and prophylactic outcome of the actives. The affinity of the spray solvent for EC can also impact drying rate, secondary drying rate (removal of residual solvent in a secondary batch process), and the glass transition temperature of the spray dried dispersion. This study is to understand the interaction of alcohol/water mixture with EC films of various molecular weight and casted from various organic solutions. These understandings can help pharmaceutical scientists design coating formulations for protection and/or modifying release of active pharmaceutical ingredients (APIs) with potential alcohol exposure or ingestion.



5. Investigating Species-dependent Surface Properties of Albumins using Inverse Gas Chromatography

Vikram Karde, Daniel Burnett, Jerry Heng, Frank Thielmann

Albumins are the most common type of globular proteins having immense physiological importance and can be used as a drug delivery carrier and stabilizer. Variations in surface properties and binding or adsorption interactions of albumins have remained a key research area. External factors like moisture or temperature can affect the structure, stability, folding and activity of albumin making them susceptible to physicochemical transformations. Temperature induced surface property variations in proteins are still far from being fully understood. Surface energy could be employed as a potential descriptor for studying these effects and interactions.

6. Investigating the effect of Protein-Excipient Ratios on Lyophile Stability and Robustness

Daniel Burnett, Frank Thielmann, Jerry YY Heng, Andrew Bright, Joshua Robinson, and Kevin Ward

Freeze drying is a common method of stabilization for protein-based therapeutics and vaccines. While

lyophilization is considered more gentle than other drying methods, proteins are often formulated with amorphous saccharides or polymers, which can serve not only to prevent denaturation during processing but also as a rigid matrix that provides some physical stabilization in the dried state. However, it has been established that environmental conditions such as temperature and humidity have a strong impact on product performance under selected storage conditions.



2018

7. Comparison of the Surface Energetics of Various Co-crystal Systems with their Physicochemical Properties

Daniel Burnett, Majid Naderi, Damiano Cattaneo, Jerry Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

Co-crystal engineering has received immense prominence in pharmaceutical formulation development. The presence of co-former as an integral part of the crystal lattice in co-crystals results in significant change in the physicochemical properties. The last two decades have witnessed wide range applications of co-crystals in fine-tuning pharmaceutically important properties such as solubility, dissolution rate, hygroscopicity, stability, mechanical properties, and etcetera. Understanding the surface properties and morphology of pharmaceutical co-crystals leads to a greater understanding of surface reactivity, which in turn can be related to stability and interactions with other solids or liquids such as water. In this study, the properties of pure API's and co-crystals were studied by investigating the crystal structure, surface energy, solubility, and dissolution rate.

8. Dynamic Vapor Sorption and Raman Spectroscopy Investigation of Competitive Hydrate-Solvate Formation

Daniel Burnett, Majid Naderi, Damiano Cattaneo, Jerry Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

Approximately one-third of organic materials show crystalline polymorphism, with a further third capable of forming hydrates or solvates. The exact polymorphic state of an active pharmaceutical ingredient may influence several physicochemical properties. In particular, the hydrate/solvate state of crystalline substances is of particular concern as different hydrate/solvate forms can affect the material solubility, dissolution rate, flowability, and compressibility.

9. Effect of Relative Humidity on the Surface Energetics of Albumins

Vikram Karde, Daniel Burnett, Jerry Heng, Frank Thielmann, Jin Wang Kwek and Srinivasulu Aitipamula

Moisture can greatly affect the structure, stability, folding and activity of protein molecules. The



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interactions of the sorbed moisture with the proteins can make them susceptible to undergo physico-chemical changes under humid conditions. These protein-water interactions get influenced by the number of polar and non-polar groups and their arrangement along the protein molecule. Water also plays an important role in hydrogen bonded networks and various hydrophilic and hydrophobic interactions. Although an important contributor for protein functionality, these water-protein interactions are still far from being fully understood. Surface energy could be employed as a potential descriptor for investigating these interactions.

10. Polymer-Solvent Interactions of Pharmaceutical Excipients for Spray Dried Dispersion

Jin Zhao, Daniel Burnett, William Porter III

An increasing number of new chemical entities suffer from poor solubility in aqueous media making drug delivery via oral solid dosage form challenging. To address this issue, formulations are increasingly relying on the use of amorphous solid dispersions of the active with an excipient. The excipient serves the function of stabilizing the active as amorphous in the solid state and acts as a nucleation inhibitor upon dissolution. The use of spray drying is one of the leading technologies for this application space. Similarly, hypromellose acetate succinate (HPMCAS) is one of the leading excipients used in spray drying. Although extensively used in spray drying, little is understood about the affinity of organic solvents for the HPMCAS polymer. The affinity of the spray solvent for HPMCAS can impact drying rate, secondary drying rate (removal of residual solvent in a secondary batch process), and the glass transition temperature of the spray dried dispersion.



11. Pectin-Keratin Composite Films for Drug Delivery: Influence of Keratin and Glycerol on their Surface Properties

Jin Wang Kwek, Daniel Burnett, Vikram A. Karde, Jerry Y.Y. Heng, Srinivasulu Aitipamula, Armando R. Garcia, Frank Thielmann

There is increasing interest in using a combination of biopolymers for dermal and transdermal delivery of drugs since they are biodegradable and mostly biocompatible. They can be better accepted by patients when they are used as thin, inconspicuous films. Pectin, as a good film forming polysaccharide, gives the film structure and provides controlled delivery of drugs. On the other hand, keratin allows healing of wounds with its excellent support for cell growth. A combination of pectin and keratin in a composite film could be advantageous in accelerating wound healing. However, the first step would be to understand the effects of keratin and a plasticizer, glycerol, in the film's surface properties such as roughness, flexibility, moisture sorption and permeability.

12. Competitive Hydrate-Solvate Formation using Vapor Sorption Methods

Daniel Burnett, Majid Naderi, Damiano Cattaneo, Jerry Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

Approximately one-third of organic materials show crystalline polymorphism, with a further third capable of forming hydrates or solvates. The ultimate polymorphic state of a material may influence several physicochemical properties including physical and chemical stability. The hydrate/solvate state of crystalline substances is of particular concern. Different hydrate/solvate forms can affect the material solubility, dissolution rate, flowability, and compressibility.

13. Understanding the Surface Energetics of Various Co-Crystal Systems

Daniel Burnett, Armando R Garcia, Jerry Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

Cocrystal engineering has been gaining prominence in pharmaceutical formulation development. Typically, the primary objective of pharmaceutical cocrystals is to create materials that have physical and chemical properties that differ from that expected of the pure API's without making and/or breaking covalent bonds. One of the most desired properties to alter is the overall material dissolution rate. Understanding the surface properties and morphology of pharmaceutical cocrystals leads to a greater understanding of surface reactivity, which in turn can be related to stability and interactions with other solids or liquids such as water. In this study, the properties of pure API's, cocrystals and physical mixtures (in same molar ratio as cocrystal) were studied by investigating the crystal structure and surface energy.



14. Surface Energetics of Pharmaceutical Cocrystal Systems

Daniel J Burnett, Armando R Garcia, Jerry YY Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

The surface properties of three different cocrystal systems were investigated and compared to simple physical mixtures. Both PXRD and IGC results indicated that the cocrystal samples had unique properties compared to the pure API and physical blends. The unique surface energy characteristics of the cocrystals could lead to desired formulation, drug delivery, or stability characteristics compared to the pure API materials.

15. Surface Energy and Physical Properties of Ibuprofen Grades

Daniel J. Burnett, Armando R. Garcia, Shaukat Ali, Yidan Lan, and Nigel Langley

The physical properties of active pharmaceutical ingredients (API) and excipients, such as solubility, particle size, and flowability, are crucial in preparation of solid dosage forms. To enhance the solubility and bioavailability of the API, micronization and surface modification are commonly introduced in pharma industries to improve these physical properties. In the recent years, many studies have been focused on understanding the mechanism of these improvement, especially on the relationship between the particle surface energy and the powder flowability. Although micronization can improve the drug's solubility, it may increase the tendency of agglomeration and reduce the flowability. Besides micronization, the particle size can be controlled by crystallization conditions. However, it is warranted to understand the surface energy of drug crystals and their impact on the processability and manufacturing of drug products. In this study, four different grades of Ibuprofen, IBP, (Ibuprofen 25, 50, 70 and 90), representing four crystallization conditions, were chosen for surface energy and physical property measurements. For comparison

16. Investigating Blend Uniformity of API/Excipient Mixtures via Surface Energy Distribution Measurements

Daniel J Burnett, Armando R Garcia, Jerry YY Heng, Frank Thielmann, Jin Wang Kwek, and Srinivasulu Aitipamula

The powder blending process is often identified as a challenging operation in solid dosage form manufacturing. On one hand, inadequate blending leads to poor active ingredient/excipient mixing. On the other hand, excessive blending could potentially deleteriously affect the drug content uniformity of the final product. Mixing behavior is complex and can be affected by various chemical and physical properties of the solid materials like density, particle size, particle shape, and surface energy. The latter is directly related to the particulate interactions in a dry powder mixture. In this study, the surface energy values of a model active pharmaceutical ingredient (API), excipient, various physical mixtures of the two, and final capsule blend have been measured and their effects on blend uniformity investigated.



17. The Surface Energy of Mannitol Polymorphs

Robert R. Smith, Daniel J. Burnett, Frank Thielmann, and Jerry Y.Y. Heng

The surface energy of solids is important as it governs a range of solid-liquid and solid-solid interactions, influencing processing-ability of powders to performance of a formulation, and is hypothesized to differ for polymorphs. This study outlines the application of surface energy mapping by Finite Dilution Inverse Gas Chromatography (FD-IGC) to determine the surface energy distributions of mannitol polymorphs.

18. Effects of Surface Energy Heterogeneity of API/Excipient Blends on Blend Uniformity

Daniel J. Burnett, Armando R. Garcia, Jerry Y.Y. Heng, and Frank Thielmann

Blend uniformity is a function of both the formulation and processing conditions. Poor uniformity generates unacceptable amounts of discarded products, resulting in significant loss of revenue to the manufacturer. Various chemical and physical properties like particle size, particle shape, and surface properties can affect mixing behavior. When large difference in these material properties exist between the active components and excipients, de-mixing effects can occur. In this study, the surface energy values of paracetamol, lactose, various physical mixtures of the two, and final capsule blend have been measured and their potential effects on blend uniformity investigated.

19. Impact of Flow Rate and Exposure Time on Humidity-Induced Crystallization of Salbutamol Sulphate

Daniel J. Burnett, Armando R. Garcia, Jerry Y.Y. Heng, and Frank Thielmann

The deposition of active ingredients, delivered via dry powder inhalers is known to be affected by the humidity in the lung. Humidity effects can cause a change in the aerodynamic particle size distribution due to hypertonic shrinkage or hypotonic growth. Other factors are agglomeration of particles facilitated by crystallization of amorphous sites on the particle surface. A similar mechanism is also dominant for the condensational growth of nanoaerosol particles in the upper airways. While these factors are well known, it is poorly understood whether the equilibrium between lung humidity and particle surface is fully established. This depends on the inspiratory flow rate and exposure time of a particle in the airways. While these factors are well known, it is poorly understood whether the equilibrium between lung humidity and particle surface is fully established. This depends on the inspiratory flow rate and exposure time of a particle in the airways. Especially in the case of agglomeration due to crystallization of amorphous sites the above-mentioned factors strongly affect the crystallization kinetics and therefore the degree of agglomeration/ crystallization. This study investigates the flow rate and exposure time dependency of water-induced crystallization of salbutamol sulphate (SS) as a model compound at high humidity.

20. Moisture Sorption Properties of Different Poloxamer Grades by Dynamic Vapor Sorption combined with In-situ Raman Spectroscopy

Daniel J. Burnett, Armando R. Garcia, Jerry Y.Y. Heng, Frank Thielmann, Yidan Lan, Shaukat Ali, Kai Zhuang and Nigel Langley

Water sorption properties are crucial for physical characterization of excipients used in pharmaceutical formulation. An important group of excipients is Poloxamers, which are nonionic triblock copolymers composed of a central hydrophobic block of polypropylene glycol, covalently linked with two hydrophilic blocks of polyethylene glycol on each side. The water sorption isotherms of Poloxamers are important because of lack of such data in the literature, and relevant to a robust formulation development. In this study, we have investigated the moisture sorption for a range of Poloxamer grades.





2014

21. Determining Surface Amorphous Content by Surface Energy Distribution Analysis

Daniel J. Burnett, Armando R. Garcia, Jerry Y.Y. Heng, and Robert Smith

Inverse Gas Chromatography (IGC) has been used to characterize numerous properties of pharmaceutical materials including surface energy and acid-base properties, glass transition temperatures, and solubility parameter for excipient selection. Historically, IGC has focused on infinite dilution conditions, making it difficult to use as a quantitative tool for surface amorphous content. Recent improvements in instrumentation and methodology have allowed IGC to be extended to a broader range of surface coverages. This allows for the potential to use IGC as a quantitative surface amorphous content tool.

22. Determining Solubility Parameters of Poloxamers by Experimental and Computational Methods

Daniel J. Burnett, Armando R. Garcia, Yidan Lan, and Shaukat Ali

The cohesive energy of a material is a parameter, which quantifies the attraction that atoms or molecules have for one another. Thus it is directly related to the stability of a material. A common method to determine this property uses the solubility parameter, which represents the square root of the cohesive energy density. Related to drug product formulation, knowledge of the solubility parameter is important to predict the magnitude of interaction between the components of formulation (i.e. miscibility, compatibility or solvent selection), which will markedly influence the drug loading in the polymeric matrix and the stability of formulation dosages. Finally, correlations have been found between the solubility parameter and oral absorption of drugs, particle adhesion, and particle agglomeration. This study investigates the solubility parameters of different Poloxamers by both computational and experimental methods. Computation methods use group contribution theories to predict the solubility parameters, while Inverse Gas Chromatography (IGC) uses retention behavior with different solvents.



2013

23. Characterization of Fenofibrate Solid Dispersion by IGC

Daniel J. Burnett, Armando R. Garcia, Yidan Lan, Shaukat Ali, Frank Thielmann, and Jerry Heng

Over 60% of new chemical entities (NCE) under development today are poorly water soluble, thus not well-absorbed after oral administration, lowering the drug's efficacy and bioavailability. Therefore, numerous strategies have been employed to increase NCE water solubility, such as solid dispersions. The ultimate goal of the solid dispersion process is usually aimed at increasing the water solubility of an active pharmaceutical ingredient (API). Therefore, the wetting behavior of the inert carrier/matrix used



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in the solid dispersion process is very important. The detailed surface energetics and surface wettability of a commonly used carrier Poloxamer have been determined using an Inverse Gas Chromatography (IGC) method in the previous study. This study was focused on the correlation between wettability and dissolution rate. A BCS type II drug, Fenofibrate was chosen as a model drug. By comparing the wettability between API and Poloxamer solid dispersion, it is possible to study how in vitro dissolution behavior is related to the surface energy and wettability.

24. Electrostatic Charging Behavior of Gelatin and HPMC Hard Capsules

Frank Thielmann, Tomohito Nakao, Toshimitsu Usui, Tohru Kokubo, Fernando Diez, Jerry Y.Y. Heng, and Daniel Burnett

Despite its high importance, electrostatic charging/ triboelectrification is still a poorly understood phenomenon in the pharmaceutical industry. Triboelectrification is caused by friction that occurs during transport, processing and testing and leads to formulation and manufacturing issues. Electrostatics also plays a major role in design and use of hard capsules. In this paper the impact of surface modifications of HPMC and gelatin capsules (via various lubricants) on triboelectric charge is investigated at different relative humidity conditions. This evaluation is complemented by a correlation to acid-base properties of the differently treated capsule types measured by Inverse Gas Chromatography (IGC).

25. Investigating the Surface Wettability of Poloxamers used for Solid Dispersions

Daniel J. Burnett, Armando R. Garcia, Yidan Lan, and Shaukat Ali

The ultimate goal of the solid dispersion process is usually aimed at increasing the water solubility of an active pharmaceutical ingredient (API). Therefore, the wetting behavior of the inert carrier/matrix used in the solid dispersion process is very important. One method to measure wettability of powders is by determining the surface energy. Surface energy provides a useful picture of the energetic situation on the surface of the carrier/matrix and shows a strong dependency on various macroscopic properties, such as dissolution. In this study, the detailed surface energetics and surface wettability of a commonly used solid dispersion excipient Poloxamer was determined using an Inverse Gas Chromatography (IGC) method.

26. A Method to Determine Loading of Drugs on Mesoporous Silica Nanoparticles

Daniel J. Burnett, Armando R. Garcia, Robert Smith, Umang Shah, and Jerry Heng

This study proposes a methodology for determining loading of a common pharmaceutical compound on mesoporous silica nanoparticles. It utilizes Thermogravimetric Analysis (TGA) to determine amount of drug lost from mesoporous silica doped with differing amounts of ibuprofen. Doping was achieved by soaking the silica in concentrated solutions of ibuprofen in hexane for varying lengths of time. The surface energy heterogeneity of differently loaded materials was also measured by Finite Dilution Inverse Gas Chromatography (FD-IGC) to show the effect of loading. Doped mesoporous materials are

of pharmacological interest for their implementation as temporally or spatially mediated drug delivery vectors. They make an excellent choice for such a material owing to their high degree of physical and thermal stabilities, their highly tunable physical properties and high degree of biocompatibility.



2012

27. Surface Energy Distribution of Milled Paracetamol

G. D. Wang, D. J. Burnett, J. Y. Khoo, F. Thielmann, J. Y. Y. Heng

This study investigates the effect of milling on surface energetics of pharmaceutical powders. Previous studies on milling have focused on surface amorphization as the major impact of micronization. Recently, we have attributed the impact of milling on surface energy change due to exposure of weakest attachment energy facets and/or particle breakage phenomena. Here, we report on a finite concentration Inverse Gas Chromatography (IGC) methodology to confirm this hypothesis which will provide further understanding on impact of processing on powder properties.

28. Characterizing the Surface Energy Distribution of Solid Pharmaceutical Formulations

Robert R. Smith, Daniel J. Burnett, Frank Thielmann, Jerry Y. Y. Heng

This study outlines the methodology to characterize the surface energy of multi-component solid pharmaceutical formulations. Previous work has not investigated the impact of powder mixing and homogeneity of the multi-component mixtures. Such a methodology proposed here has the potential to provide for further understanding and optimization of multicomponent powder mixture properties.

29. Correlating Surface Energy and Wettability Measured by IGC to Dissolution Properties of Dry Powder Inhaler Formulations

Daniel J. Burnett, Armando R. Garcia, Jerry Y.Y. Heng, George D. Wang, Frank Thielmann, and Jason McConville

To deliver drug substances to the lung via the inhalation route, it is common to reduce the primary particle size of the active ingredient. There are different methods to produce smaller primary particles, such as micronization or spray drying. These high-energy processes often change the physicochemical properties of the API, which can ultimately alter final product performance. This study investigates the surface energy and wettability of spray-dried and micronized budesonide powders by Inverse Gas Chromatography.



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30. Prediction of Electrostatic Charging Behavior of Medical Device Polymers

Frank Thielmann, Piyush Kumar Kudar, Jerry Y.Y. Heng, and Daniel Burnett

Electrostatic charging is an often neglected but important phenomenon in the pharmaceutical industry. Especially the triboelectrification of powders and polymers due to friction that occurs during transport, processing and testing is a well-known but poorly understood problem that leads to formulation and manufacturing issues. A simple way to estimate the charge propensity of a material is the triboelectric series which gives a general ranking how materials charge against a metal standard. This ranking can help to understand how two materials charge when in contact with each other. In this study the triboelectric charge of various polymers, used in the screening of polymers during medical device development, is investigated. This evaluation is complemented by a correlation to acid-base properties of the polymers measured by Inverse Gas Chromatography (IGC).



31. Effects of Fines Addition on the Surface Energy of Lactose

A. E. Jefferson, Gerald A. Hebbink, D. J. Burnett, F. Thielmann, and J. Y. Y. Heng

Pulmonary drug delivery is an attractive way of administering medication for lung diseases like asthma and COPD. Lactose is a widely used carrier particle for pulmonary drug delivery. Physico-chemical properties of carrier particles are thought to be crucial in determining the performance of carrier-based dry powder inhalation formulation. Addition of fines (small particles of lactose) have been reported to result in carrier formulation. an improved fine particle dose or fine particle fraction of the active drug. However, the mechanism by which the fine particles alter the performance of the formulation has remained elusive. Here, we seek to investigate the effects of addition of fines on the surface energy and its overall adhesion property, and more importantly the surface energy distribution, of lactose crystals, as measured by inverse gas chromatography (IGC).

32. Surface Energy Distributions and Dissolution Rate of Aspirin

A E. Jefferson, George D. Wang, D. J. Burnett, F. Thielmann, and J. Y. Y. Heng

Particle processing such as milling may result in the preferential exposure of the weakest attachment energy facet. In this study, a finite concentration inverse gas chromatography approach is utilized to map surface energy heterogeneity of milled aspirin. A computational model for adsorption from the gas phase onto a heterogeneous surface based on Henry's Law isotherm is used to obtain surface energy distribution data, to describe changes in dissolution rate of a milled aspirin sample.

33. Using Dispersive Surface Energy and Effective Amorphous Surface Area to Quantify Surface Amorphous Content

Daniel J. Burnett, Armando R. Garcia, Rachael Forcino and Jeff Brum

Inverse Gas Chromatography (IGC) has been used to characterize numerous properties of pharmaceutical materials including acid-base properties, glass transition, temperatures, and solubility parameters. For partially amorphous materials, IGC at infinite dilution has raised questions about the contributions of the amorphous and crystalline sites to the measured surface energies. Previous work has looked at effective surface energy of heterogeneous mixtures. This study extends that concept by combining surface energy data with the Effect Amorphous Surface Area (EASA) to quantify surface amorphous content.

34. Humidity and Temperature Stability Window for Spray-Dried and Freeze-Dried Biopharmaceutical Powders

Daniel Burnett, Armando R. Garcia, and Majid Naderi

Biopharmaceutical materials are commonly spray-dried or freeze-dried in solid form at some point in the development. This often creates high amounts of amorphous material. However, amorphous materials are inherently metastable and therefore tend to revert to a more thermodynamically stable, crystalline form. As this instability has a potentially negative impact on storage and drug potency it is important to quantify the amorphous content of pharmaceutically relevant materials. Humidity can often act as a plasticizing agent, thus increasing molecular mobility and accelerating phase change.



35. Milling Effects on the Aspect Ratio and Surface Energy Heterogeneity for Mannitol

Daniel J. Burnett, Majid Naderi, Raimundo Ho, Jerry Y.Y. Heng, Frank Thielmann, Adam Keith and Greg Thiele

Crystalline materials can be energetically anisotropic, meaning the surface chemistry is not homogeneous or different crystal planes can exhibit different chemistry. Therefore, even for crystalline materials, it is important to treat them as energetically heterogeneous materials, and their surface energy may not be adequately described by a single value. Finite concentration Inverse Gas Chromatography (IGC) experiments allow for the determination of surface energy distributions which more accurately describe the anisotropic surface energy for real materials. Previous studies have investigated the anisotropic nature of mannitol. In this study, we investigate the effects of milling on the heterogeneity of crystalline D-mannitol. In addition, the particle aspect ratio as a function of milling will be correlated to the surface energy heterogeneity and different crystal planes.

36. Milling-Induced Changes in Active Site Distribution of Budesonide

Daniel J. Burnett, Frank Thielmann, Raimundo Ho and Jerry Y. Y. Heng

To deliver drug substances to the lung via the inhalation route, it is common to micronize the active ingredient to reduce particle sizes. These high-energy processes often change surface morphology, increase defect sites and decrease crystallinity. This affects the interaction between particles in a drug substance blend with lactose due to changes of the surface energy distribution. The surface energy is an important contribution to the overall adhesion/ cohesion balance in a physical dry powder blend and can therefore impact stability and pharmaceutical performance.¹ This study investigates the change of the surface energy distribution before and after air jet milling of budesonide using Inverse Gas Chromatography (IGC).

37. Inverse Gas Chromatography: A Methodology for Determination of Surface Energy Heterogeneity

A. E. Jefferson, R. Ho, D. J. Burnet, F. Thielmann, and J. Y. Y. Heng

The surface energetics of powders is of fundamental and practical importance in understanding the performance of pharmaceuticals (eg. solubility, adhesion, colloid stability, powder flow, mixing performances and product performance). Here we present a methodology based on finite concentration inverse gas chromatography (IGC) for the determination of surface energy distribution of particulates and a theoretical approach to interpret and determine the distribution of surface energy.



38. Dynamic Vapor Sorption as a PAT Tool to Assess Tablet Coating

Juana Vieta, Armando R. Garcia and Dan Burnett, Darius Dubash, Eva Heintz, Bradley Clark and Umang Shah

Employ Dynamic Vapor Sorption (DVS-Intrinsic, Surface Measurement Systems-London UK) as a PAT tool to assess the moisture protection imparted by various tablet film coating materials and coating process parameters employed.

39. Determining Low Levels of Amorphous Content using Vapor Sorption Methods

Frank Thielmann and Daniel Burnett

Amorphous materials are inherently metastable and therefore tend to revert to a more thermodynamically

stable, crystalline form. As this instability has a potentially negative impact on storage and drug potency it is important to quantify the amorphous content of pharmaceutically relevant materials.

40. Comparison of Different Techniques to Measure the Surface Roughness of Pharmaceutical Powders

Daniel Burnett, Frank Thielmann, and Jerry Heng

Surface roughness of pharmaceutical solids has importance for several reasons. For instance, in dry powder formulation development, the surface roughness of carrier particles has been shown to affect drug product in vitro performance. Additionally, surface roughness can influence tablet compression pressure and adhesion of coatings. Therefore, it is important to quantitatively measure the degree of surface roughness. There are several techniques available for measuring surface roughness. Different techniques may preferentially measure roughness over different domains (i.e. macro roughness, micro roughness, or nano roughness).



41. Solvent-Induced Crystallization of Micronized Drugs

Daniel Burnett

Drug substances intended for drug delivery to the lungs typically require particle size reduction. High energy processes are typically utilized to produce particles smaller than 10 μm but these processes are also known to influence crystallinity, which can lead to a reduction in physical and sometimes even chemical stability. Therefore, these materials may be conditioned following micronization before further processing. Such a "deamorphization" step typically involves the treatment of the materials with an appropriate solvent that plasticizes the material and induces crystallization. While the selection of the solvent is critical, the degree of control over the deamorphization process is also very important. A treatment time that is too short may lead to incomplete crystallization of the material, while overtreatment may cause partial dissolution and agglomeration. In order to estimate the appropriate treatment time, knowledge of the crystallization kinetics is required.

42. Role of Powder Surface Properties in High Shear Wet Granulation

Raimundo Ho, Jerry Y.Y. Heng, Frantisek Stepanek, Sarah E. Dilworth, Daryl R. Williams

High shear wet granulation is a very important but poorly understood unit operation in solid processing industry. The lack of fundamental understanding in the process means that obtaining a quantitative relationship between formulation, process operating conditions and the final granular product

performance is extremely difficult. This study focuses on the importance of powder surface energetics (wettability) or surface chemistry and the relationship to granule properties. Three model materials with markedly different surface chemistries were characterized and granulated under identical conditions to observe changes in the final granule size. A novel technique using Inverse Gas Chromatography (IGC) to characterize surface energy distributions of particulate pharmaceuticals is also employed and described here.

43. Using IGC to Monitor the Energetic Relaxation of Milled Budesonide

Daniel J. Burnett, Armando R. Garcia, and Frank Thielmann

Drug substances that are intended for delivery via the lung are often micronized to reduce the particle size to the respirable range of below 6 μm . These high-energy processes often change surface morphology, increase defect sites, or decrease crystallinity. It is important to understand how these high-energy sites relax over time at different storage/exposure conditions. This study monitors the surface chemistry of a milled budesonide sample after exposure to 52% relative humidity and 25 °C as a function of exposure time using Inverse Gas Chromatography (IGC).



44. Impact of Freeze-Drying Conditions on the Stability of Protein-Saccharine Formulations

Daniel Burnett, Frank Thielmann, Kevin Ward, and Isobel Cook

Proteins are commonly freeze-dried in combination with stabilizers such as amorphous saccharides. However, environmental conditions such as temperature and humidity also have a profound impact on product performance and storage properties. Freeze-drying conditions can significantly affect the ultimate lyophile stability, its dryness, morphology, porosity and surface area. An increase in moisture content or temperature may cause a glass transition and crystallization of the sugar resulting in a loss of thermal stability of the protein. For this reason, knowledge of physico-chemical properties such as glass transition and water sorption behavior is important.

45. Impact of Humidity on Drug - Propellant Interactions in Metered Dose Inhaler Systems

F. Thielmann, M. Naderi and Peter Jannick

Due to the relatively low solubility of most drugs in HFA's most MDI's are suspension-based. The stability of these drug suspensions depends strongly on the drug-drug as well as the drug-propellant interaction. The small drug particle size required for deep lung deposition (usually <5 μm) is associated with high surface energies causing aggregation of the drug particles. For this reason, drug-propellant interactions

need to be sufficiently strong to keep the drug in suspension and avoid aggregation or deposition on the container walls. Inverse Gas Chromatography (IGC) allows for a direct measurement of drug-propellant interaction. Interactions were also studied at different background humidity to investigate the impact of environmental humidity and residual moisture content of drugs on drug-propellant interactions.

46. Mucoadhesive hydrogel films based on blends of poly(acrylic acid) and methylcellulose for Buccal Drug Delivery

Olga V. Khutoryanskaya, Vitaliy V. Khutoryanskiy, Majid Naderi, Daniel J. Burnett

Buccal drug delivery has recently become an important route of drug administration. The purpose of this work was to develop mucoadhesive hydrogel films by blending poly(acrylic acid) (PAA) and methylcellulose (MC) with subsequent cross-linking and correlate their adhesion properties to the sample characteristics.



47. Quantifying Low Levels of Amorphous Theophylline and Carbamazepine without Standards

Frank Thielmann and Daniel Burnett

Amorphous materials are inherently metastable. Therefore, the presence of amorphous regions in pharmaceutical solids can lead to formulation, processing, and storage challenges. Amorphous phases can be created intentionally (i.e. freeze-drying) for desired properties such as increased solubility or bioavailability. Or, amorphous regions can be introduced unintentionally during processing (i.e. milling). Regardless of how the amorphous regions are created, it is important to fully characterize these materials throughout the product's development cycle.

48. The Affect of Processing Steps on the Polymorphic State of Common Pharmaceutical Sugars

F. Thielmann, D. Burnett, and N. Jovanovic

Proteins are often formulated with sugars to stabilize the solid form. The polymorphic state of these sugars may influence several physicochemical properties of the final formulation including physical and chemical stability. Also, the polymorphic state of sugars can affect drug-carrier interactions which, in turn, can affect processability (i.e. powder flow and content uniformity). Different processing routes may affect the ultimate polymorphic form; therefore, it is vital to track any changes in form during steps in the production process.

49. Investigation of Carbamazepine/ Solvate Formation over a Range of Temperatures using Vapour Sorption Techniques

Frank Thielmann and Daniel Burnett

Physical and chemical stability of pharmaceutical solids is highly dependent on its polymorphic state. For example, the solvate state of crystalline substances is of particular concern. The ultimate solvated state can be dependent on both temperature and concentration of the solvate vapor. Also, different solvate forms can affect the material solubility, dissolution rate, flowability, and compressibility. For the above reasons, it is paramount to study the solvate behavior over a wide range of storage and processing conditions.

50. The Effect of Primary Particle Surface Energy on Agglomeration Rate in Fluidized Bed Wet Granulation

F. Thielmann, M. Naderi, M. Ansari, and F. Stepanek

The wet granulation of pharmaceutical materials typically involves the co-agglomeration of small crystals of a drug substance with particles of an excipient by means of a liquid binder. It is well known that granulation behavior can be rather sensitive to the properties of the primary solid particles. For this reason, the effect of particle surface properties (wettability and surface energy) on the rate of agglomeration in a fluid-bed top-spray granulation process is investigated.



51. Impact of Protein Concentration on the Glass Transition Behavior of Protein-Sugar Formulations

Majid Naderi, Frank Thielmann, Andrew Ingham and Kevin Ward

Due to the significant increase of protein-based therapeutic applications in recent years the formulation of proteins has become an area of high interest. A common method is the freeze-drying of proteins embedded in amorphous structures formed by sugars. Although these sugar matrices provide some stabilization, environmental conditions such as temperature and humidity have a strong impact on product performance and storage. An increase in moisture content or temperature may cause a glass transition and crystallization of the sugar resulting in a loss of thermal stability of the protein. For this reason, knowledge of physico-chemical properties such as glass transition and water sorption behavior is important. In this study the impact of water sorption and glass transition behavior of various bovine serum albumin (BSA) - sugar formulations have been studied.

52. Determining the Critical Relative Humidity for Moisture-Induced Phase Transition

Daniel Burnett and Frank Thielmann

Low molecular weight amorphous materials will typically revert to their more stable crystalline state over a certain temperature range. To complicate matters, ever-present water vapor can have a significant effect on amorphous materials. Sorbed water often acts like a plasticizing agent, thus significantly lowering the glass transition temperature (T_g) causing spontaneous phase transitions and lyophile collapse. Therefore, determining the necessary threshold temperature and humidity conditions to prevent a glass transition is critical for storage and processing of amorphous materials. In this study the humidity at which the glass transition occurs was determined for spray-dried lactose and spray-dried salbutamol sulphate.

53. Investigation of Hydrate and Solvate Behavior using Vapor Sorption Techniques

Daniel Burnett and Frank Thielmann

The ultimate polymorphic state of a material may influence several physicochemical properties including physical and chemical stability. The hydrate/solvate state of crystalline substances is of particular concern. Different hydrate/solvate forms can affect the material solubility, dissolution rate, flowability, and compressibility. By one estimate, approximately one-third of all pharmaceutical actives are capable of forming crystalline hydrates. For these reasons, there is increased pressure to fully characterize and control the polymorphic form of excipients and active drugs. For many materials, phase transitions can be influenced by the amount of solvent vapor surrounding the sample. This study describes how vapor sorption techniques can be used to detect and characterize hydrate/solvate formation as a function of solvent partial pressure.

54. The Characterisation of Adhesion Properties of Powders by a Dynamic Gravimetric Vapour Sorption Approach

Frank Thielmann and David Fetsch

The measurement of the surface properties of powders is of increasing importance to many industries, which depend upon powder processing or powder technology. If known, the surface energy of a powder may be used to predict a wide range of properties such as processing stability, adhesion, colloid stability, toughness, powder flow and product performance. In practice the measurement of the surface energy of powders is non-trivial and prone to potentially large errors or uncertainties despite a wide range of techniques being available. In this paper we present a dynamic gravimetric method for determining the work of adhesion of powders by measuring the adsorption isotherm of organic vapors using a dynamic gravimetric vapor sorption method. This approach avoids the limitations inherent in many of the currently available methods, such as wettability.

55. Understanding the Impact of Magnesium stearate on the Process Behavior of Dry Powder Formulations

F. Thielmann, D. Burnett and Duncan Pearse



Magnesium stearate is a well-known force control agent for lactose and other excipients used in dry powder formulations. It is common knowledge that it improves processability in general and powder flowability in particular. However, despite all advances in the understanding of dry powder formulations the basic physico-chemical factors dominating the interaction between lactose and magnesium stearate are still unclear. For this reason, this paper investigates this interaction and tries to elucidate the fundamental mechanism by measuring surface heterogeneity profiles using Inverse Gas Chromatography (IGC). The figure below shows a typical set-up for an IGC experiment. The column is packed with the material under investigation and known vapor phase probe molecules are injected. The retention time of these vapors allow conclusions about the energetic situation of the surface of the solid.

56. Correlation of Polymer Energetics and Drug Release Rates

F. Thielmann, D. Burnett, S. Baumgartner, O. Plainness, J. Kristl

Cellulose ether polymers are common matrix compounds in sustained release tablets. It was shown previously by Inverse Gas Chromatography (IGC) that drug release from polymer matrices with a high polarity was faster due faster polymer swelling and chain relaxation. IGC is a well-established technique for quickly and accurately measuring the surface energetics for a wide range of solids. The goal of this study is to investigate polar and non-polar interactions of the polymers further as well as the influence of drug based on surface energy measurements of the individual formulation components and to correlate results with drug release profiles of the final product.



57. Investigating the Kinetics of Moisture-Induced Crystallization of Amorphous Lactose by Dynamic Vapor Sorption (DVS)

Daniel Burnett and Frank Thielmann

Lactose is an often-used excipient in food and pharmaceutical applications. Due to its polymorphism the understanding of its recrystallisation behavior under different humidity and temperature conditions is important. The crystallization of sprayed- dried lactose around the glass transition has been investigated in this study. Many low molecular weight amorphous materials will revert to their thermodynamically stable, crystalline form. The timescale of this transition is dependent on both temperature and humidity (or solvent partial pressure). Therefore, understanding the kinetics of this transition over a wide range of temperatures and relative humidity (RH) values is important for the processing and storage of materials containing amorphous phases.

58. Moisture-Protective Polymer Coatings: Water Uptake Behavior Analyzed by Dynamic Vapor Sorption

Drug degradation is a commonly encountered problem in solid pharmaceutical dosage forms containing herbal drugs. Degradation could result from contact with atmospheric moisture from residual water. For example, garlic powder contains moisture-sensitive components, which tend to degrade during storage. In this study, the herbal drug was freeze-dried to minimize the residual water content and compressed into tablets. The latter were coated with Opadry AMB (a polyvinyl alcohol-based formulation), Methocel E5 (hydroxypropyl methylcellulose) or Eudragit E PO (a polyacrylmetacrylate) to reduce water uptake during storage. To study the water uptake kinetics of tablets coated with different moisture protective polymers and of the polymers themselves by dynamic vapor sorption (DVS). To physicochemically characterize the systems during storage at elevated relative (RH).

59. Correlation of Wet-Granulation Behavior and Surface Energy Results Obtained by Inverse Gas Chromatography

F. Thielmann, D. Burnett, K.M. Lusvardi, and T. Durig

Controlling the adhesive strength between active drugs and binding agents is paramount in developing successful pharmaceutical formulations. For instance, poor drug-binder adhesion can lead to insufficient binder spreading and inferior granule and tablet mechanical properties. Therefore, the ability to predict drug-binder strength will be a valuable tool for designing tailored drug systems.

60. Variation in Crystalline Paracetamol Surface Properties Due to Milling

Jerry Y. Y. Heng, Frank Thielmann and Daryl R. Williams

In this study, surface energies of particulate paracetamol: milled and unmilled crystals of varying size fractions have been investigated by Inverse Gas Chromatography (IGC).



61. Characterizing the Amorphous State in a Pharmaceutical Powder using an Automatic Moisture and Organic Vapor Analyzer

Daniel Burnett and Frank Thielmann

Amorphous materials in pharmaceutical formulations yield complex and challenging problems concerning the performance, processing, and storage of these products. The presence of amorphous materials can be wanted or unwanted, depending on the desired or undesired unique properties of the amorphous phase. For these reasons, fully characterizing the amorphous state is critical in the

formulation of pharmaceutical powders.

62. A New Method for the Determination of Hydrophilicity of Drugs and Excipients (iGC)

Frank Thielmann, Majid Naderi and Manaswini Acharya

The measurement of hydrophilicity and hydrophobicity of pharmaceutical powders is important for a better understanding of wet-granulation, bioavailability etc. Usually these parameters are characterized by their partitioning coefficient in water/octanol ($\log(p)$ value) or water contact angle measurements. The latter method is known to be inaccurate for powdered samples while the former suffers from the fact that the solid under investigation needs to be soluble. For this reason, an alternative method is required.



63. An Investigation of the Adsorption Mechanism of Process Solvents on Pharmaceutical Excipients by Dynamic Vapor Sorption (DVS)

Frank Thielmann and Daniel Burnett

The interaction of organic solvents and water with pharmaceutical powders is highly important for the understanding of solvent-based processes, e.g. wet-granulation, crystallization etc. For this reason, information about the adsorption mechanism of these solvents on powder surfaces is required. A fast and easy way of investigating the mechanism is the determination of sorption isotherms.

64. Determining Small Amorphous Contents of Pharmaceutical Powders using the Sorption Properties of Organic Vapors by Dynamic Vapor Sorption

Frank Thielmann and Daniel Burnett

Amorphous materials in pharmaceutical formulations yield complex and challenging problems concerning the performance, processing, and storage of these products. The presence of amorphous materials can be wanted or unwanted, depending on the desired or undesired unique properties of the amorphous phase. Also, during the processing of pharmaceutical solids (e.g. milling, spray drying, tablet compaction, wet granulation and lyophilization), various degrees of disorder in the form of crystal defects and/or amorphous regions may be generated. Even relatively low levels of amorphous material (<10%), may have a detrimental impact on the stability, manufacturability and dissolution characteristics of the formulated drug product. For these reasons, determining the amount of amorphous material is critical in the formulation of pharmaceutical powders.

65. Investigation of Batch-to-Batch Variations in the Dissolution Rate of an Active Pharmaceutical Ingredient (API) by Inverse Gas Chromatography (IGC)

Frank Thielmann, Simone Reutenauer and John Booth

Batch-to-batch variations of API's pose an important problem in drug manufacturing. The choice of techniques available for the characterization and identification of different batches is limited due to the small physiochemical differences which require a highly sensitive technique.

66. The Study of Drug-Carrier Interactions by Inverse Gas Chromatography (IGC)

Frank Thielmann and Duncan Pearse

The study of drug-carrier interactions is highly relevant to pharmaceutical applications. The interaction between active drug and carrier may be too strong, resulting in an inefficient release of the drug. In the opposite case, weak interaction, the release of the drug might occur before the targeted area is reached. It is for this reason that an accurate prediction of the magnitude of drug-carrier interaction is of interest.

67. Determination of Surface Energy Heterogeneity Profiles of Magnesium Stearate Modified Lactose by Inverse Gas Chromatography

Daniel Burnett, Frank Thielmann and Duncan Pearse

For many pharmaceutical applications it is desirable to characterize the entire surface energy profile, both high and low energy sites, of a solid material. This is particularly useful for understanding the sorption mechanisms and the prediction of the interaction at interface boundaries of blends and composites. In this study, surface energy profiles of Lactose and Magnesium stearate have been determined using IGC.



68. The Determination of Low BET Surface Areas of Pharmaceutical Materials by Dynamic Vapor Sorption (DVS)

Frank Thielmann and Daniel Burnett

The BET surface area is an important parameter in the characterization of pharmaceutical materials. Standard static- volumetric methods usually involve the measurement of isotherms with nitrogen at 77 K in a vacuum system. However, this method is time consuming and provides only limited information on materials with surface areas smaller than 1 m²/g. Therefore, a method is desired which provides quick

and reliable isotherm measurements for small surface area materials at ambient pressure and temperature.

69. A New Approach for the Determination of Low Amorphous Contents by Inverse Gas Chromatography (IGC)

Frank Thielmann

Small amorphous contents of pharmaceutical materials are difficult to determine using conventional methods. XRD doesn't perform reliable measurements below 10% of amorphous material. Standard microcalorimetry and vapor sorption require mixtures of purely amorphous and crystalline material for calibration. Therefore, a sensitive method is required that is independent of calibration standards.

70. The Determination of Solubility Parameters by Inverse Gas Chromatography (IGC)

Frank Thielmann and Simone Reutenauer

Solubility parameters are directly related to the cohesive energy density of a material which in turn is a measure of the strength of interaction between molecules and atoms. Therefore, solubility parameters can be used to predict drug or excipient stability. Moreover, correlations have been found between the solubility parameter and oral absorption of drugs, thus a methodology to accurately measure solubility parameters would be most welcome in the pharmaceutical industry.



71. The use of Inverse Gas Chromatography (IGC) to Measure Surface Properties of α -Lactose Monohydrate under Humidified Condition

Helen E Newell, Graham Buckton, David A Butler, Daryl R. Williams

These experiments were designed to investigate the use IGC to probe the nature of a surface exposed to different relative humidities (%RH). In order to achieve this objective, an instrument was specially designed and built by SMS Ltd. The potential of this new experimental design was explored, concentrating especially on the validation and reproducibility of the instrument. The substrate chosen for investigation was α -lactose monohydrate. This was for several reasons, not least the amount of previously published literature on this substrate, both by IGC at 0 %RH and by other techniques over the humidity range. We aim to extend this knowledge by investigating the effect of humidity on the dispersive surface energy of α -lactose monohydrate, and to open up a new field of investigation for IGC.