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MIBio 2015

Stability of biopharmaceuticals

From molecular interactions to successful products

Wednesday 21st October 2015
Magdalene College, Cambridge

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MIBio 2015 is organised by the Formulation Science and Technology Group (FSTG) and the Joint Colloids Group of the SCI and Royal Society of Chemistry (RSC) together with the Academy of Pharmaceutical Sciences (APS), with valuable assistance from the Knowledge Transfer Network (KTN).

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The Formulation Science and Technology Group is a subject group of the Royal Society of Chemistry, London. It is the leading scientific organisation dedicated to product formulation. As a charitable organisation, it works for the benefits of its members and to further the awareness of formulation science. It fosters the advancement of formulation science across many scientific disciplines and industrial applications, including pharmaceuticals, cosmetics, foods and detergents. It is a point of focus for all industrialists and academics engaged in the practice of formulation science. The FSTG organises many events during the year for the benefit of its members, including conferences, training days, and networking events.

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Colloid science today is a very broad and dynamic subject spanning a wide range of areas from classical dispersions to novel nanoparticles for drug delivery. The Colloid Group aims to act as a focus for these interests for the UK colloid community (and wider). Whether you are a chemist, physicist, engineer, student, formulation scientist, nanotechnologist, pharmacist, biologist, polymer scientist, food scientist or any other related discipline interested in colloids, we invite you to join the Colloid Group. Today the group supports the UK colloid community by organising a range of meetings ranging from one day to multiday meetings. We also invite nominations for outstanding contributions to colloid science in the UK through our three awards, the McBain Medal, the Thomas Graham Lecture and the Rideal Award.

For more information visit: **www.colloidsgroup.org.uk**

Stability of biopharmaceuticals

From molecular interactions to successful products

Foreword

Stability of biopharmaceuticals

From molecular interactions to successful products

It is a pleasure to welcome you to the 5th annual MIBio conference at Magdalene College, Cambridge. The aim of the MIBio series is to bring the biopharmaceutical formulation community together to discuss the latest developments in the field.

Over the last decade, formulation has become a critical and integral part of the biopharmaceutical development process. With the increasing number of pipeline products and off-patent biologics, the importance of formulation is even greater than ever. We believe that in order to ensure future progress the industrial and academic communities need to work together, so we are delighted to welcome a very healthy mix of academics and industrialists at our event today.

Each year, the MIBio conference has a special theme. This year, the discussion will focus on the most efficient ways of integrating the latest scientific and methodological advances in the formulation process and, in turn, optimal ways of integrating formulation development into the creation of a successful biopharmaceutical product. The best ways of extracting value from such advances via the creation of new intellectual property will also be addressed. Seven key experts in the field will present on these topics during the day and, as is traditional in the MIBio series, there will be opportunities for audience participation in the discussion of these important matters.

We are very grateful to all the sponsors and exhibitors who have made this meeting possible. We also thank all the authors who sent in abstracts and are contributing to the poster session.

MIBio 2015 is a one-day event, but the discussions you start today may lead to new collaborations and discoveries that will help steer the development of the next generation biopharmaceutical products.

We hope you enjoy the event,

Jan Jezek, Nicholas Darton, Tejash Shah and **Stephen Harding**
on behalf of MIBio 2015

MIBio 2015

MIBio 2015 Programme

08:00 Registration opens

09:00 Opening remarks

Morning session, *chaired by* Nicholas Darton (Arecor, UK)

09:15 Drug discovery – recent trends
Alan Smith (Cambridge in America, former CSO Genzyme, USA)

09:45 Measuring changes to the hydration water around proteins by terahertz spectroscopy
Chris van der Walle (MedImmune, UK)

10:15 Speed Networking

11:15 A novel in vitro method to model the fate of subcutaneously administered biopharmaceuticals and associated formulation components
Randy Mrsny (University of Bath, UK)

11:45 Exhibitors highlight

12:30 Lunch Break, Exhibition and Posters

Afternoon session, *chaired by* Bernardo Perez-Ramirez (Genzyme, USA)

13:45 Introduction

14:00 Starting with the end in mind. New approaches to biopharmaceutical development to reduce product attrition
Andreas Arnell (Lonza, UK)

14:30 The devil you know: look early, look hard and minimize the unexpected
Mark Krebs (Biogen, USA)

15:00 Coffee break, Exhibition and Posters

15:30 Formulation Patents for Biologics: Challenges and Strategies for Innovators and Biosimilar Developers
Tim Shea (Sterne, Kessler, Goldstein & Fox, USA)

16:00 Discussion panel: Value of formulation throughout the product life – successful products, life cycle management & intellectual property

17:00 Concluding remarks

17:10 Conference ends

Morning Session - Lecture Abstract

Drug Discovery – Recent Trends

Alan E Smith - Chairman, Cambridge in America, USA

The process of discovering novel drugs to treat human disease is, and always has been, an extremely difficult endeavour – it takes many years, costs a great deal of money and most candidates fail. Further, in spite of 50 years of spectacular progress in the biological sciences, the rates of success at drug discovery have not improved, so much so, that almost all major pharmaceutical companies have abandoned their early in house efforts and now seek to outsource the discovery process. This provides great opportunity for start-up companies, but whether outsourcing will prove more cost effective overall remains to be seen.

Another trend in biotech and pharma is the emergence of so-called rare diseases as a major, now universal emphasis. Given that the molecular basis of some of these diseases has been elucidated in humans, and that treatments are often replacement rather than interventional, the probability of success developing a drug has proved somewhat greater. However given the small number of patients, such drugs are necessarily very expensive.

Detailed analysis of several diseases, such as breast cancer, has revealed that the underlying mechanism comprises several different molecular mechanisms. This has spawned the notion that all diseases are rare diseases and gives rise to optimism that over time new drugs might be developed for each individual mechanism. However such treatments, though having a higher likelihood of successful treatment effects, will also be very expensive. Overall although each rare disease mechanism affects only a few patients, collectively the cost of treating such diseases will become prohibitive. Fortunately, alternative approaches such as harnessing the immune system to attack cancers more generally appear to be having some success.

Biotechnology stocks have performed very strongly for over 5 years, so much so we appear to be in another bubble. Company valuations and IPOs have reached extraordinary levels. Although some analysts have argued otherwise this is unlikely to be sustained.

All recent trends underline the value of formulation a low risk approach to enhancing the activity and value of drugs that we already know are effective in patients. The process of developing completely new drugs will remain extremely challenging for the foreseeable future. Enhancing the activity of those already proven to be effective will be a valuable contribution for years to come.

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Morning Session - Lecture Abstract

Measuring changes to the hydration water around proteins by terahertz spectroscopy

Chris van der Walle - MedImmune, UK

Terahertz time domain spectroscopy (THz-TDS) provides insight into the interaction between proteins and water, or 'hydration shell', by analysing the nonlinear relationship between protein concentration and THz absorption. Distinct changes in THz absorption were observed for mAbs formulated up to 150 mg/ml in different excipients: NaCl, sucrose, proline and arginine. Relating these changes to key formulation parameters such as viscosity will improve our understanding of mAb behaviour at high concentrations.

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Morning Session - Lecture Abstract

A novel in vitro method to model the fate of subcutaneously administered biopharmaceuticals and associated formulation components

Randall J. Mrsny - Department of Pharmacy and Pharmacology, University of Bath, Bath, UK

At present, subcutaneous (SC) injection is the primary method of self-administering biopharmaceuticals such as insulin and monoclonal antibody therapies. There is no current in vitro method available, however, to pre-screen biopharmaceutical formulation performance prior to in vivo studies. Further, there is no animal model that predicts in vivo outcomes in man for biopharmaceutical formulations, leaving formulation scientists with a paucity of methods to examine the potential performance of formulations intended for SC injection. We address this issue by the development and validation of a novel in vitro system, termed Scissor for Subcutaneous Injection Site Simulator, which allows assessment of biopharmaceutical fate as it experiences the dynamic transition from its formulation conditions to the homeostatic environment of the hypodermis. The system uses a dialysis-based chamber that can contain non-cellular extracellular matrix (ECM) components positioned in a bicarbonate-based buffer chamber to emulate the SC injection site and physiological conditions imposed by the infinite sink of the body, respectively. Here we validate the Scissor using the ECM element hyaluronic acid in the context of insulin and monoclonal antibodies following their SC injection. Our findings suggest that Scissor may provide a rapid and tractable method to assess the possible fate of an injected biopharmaceutical that could be used as an alternative to animal testing for the early screening of formations intended for SC injection.

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Afternoon session – Lecture Abstract

Starting with the end in mind. New approaches to biopharmaceutical development to reduce product attrition

Andreas Arnell - Lonza UK

Biopharmaceutical development seems to be fraught with risk. For every ten candidates that enter the clinic, only one is likely to be successful. The primary cause of failure is insufficient efficacy, yet other causes such as limitations of the pharmacology or bioavailability, safety or toxicology issues, or even stability and quality issues cannot be discounted. Even given clinical success, market success is increasingly seen as being dependent on ease of use factors such as frequency of administration and delivery route. Long acting or sub-cutaneous self-administrated drugs puts an onus on high concentration, long term stability, viscosity and, by implication, the formulation.

Rather than determining the final presentation of the drug at a late stage; the characteristics that enable it can be designed into the drug during pre-clinical development. Starting with the end in mind we can trace the final quality target product profile (QTTP) back through the formulation and process development stages to key characteristics of the drug molecule itself. By performing a 'Developability Assessment' of the protein we can aim to understand some of the inherent determinants of quality, safety and efficacy. This presentation will discuss new risk assessment approaches utilising in silico platforms and surrogate in vitro assays to evaluate product "Developability".

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Afternoon session – Lecture Abstract

The devil you know: look early, look hard and minimize the unexpected

Mark Krebs - Biogen, USA

Formulation space is multidimensional, not only in terms of formulations that can be explored, but also in terms of properties that need optimizing. For early stage programs, striking the balance between speed and thoroughness is often difficult. Going into the clinic, and failing more quickly, is advantageous, but so is minimising future optimisation work, when changes are often more costly. To enable quick decision-taking while still learning about the molecule, we have established a platform set of questions we ask of our molecule. Performed at a stage when research still have multiple candidates, we can rank the candidates and for each develop a risk profile: what are the degradation pathways and how do they compare between candidates? Additionally, information is collected about the pH range and basic excipients that result in the least degradation. This information is then used to fine-tune our first-in-human formulation work. A third study with more representative, pilot-scale derived material is then used to confirm the previous findings and lead to formulation nomination.

In this presentation I will show how we layer our stability-indicating work and how we use the results from one set of assays to inform the next. Throughout I will illustrate with examples from different projects this and earlier versions of this approach have been applied to.

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Afternoon session – Lecture Abstract

Formulation patents for biologics: challenges and strategies for innovators and biosimilar developers

Tim Shea - Sterne, Kessler, Goldstein & Fox, USA

Formulations patents are typically viewed as less strong in comparison to the original composition of matter patents covering a novel NCE or NME. Nevertheless, formulation patents are a critical component of any patent portfolio surrounding a valuable therapeutic product, particularly biologic products. This presentation will focus on the role of formulation patents in patent life cycle management strategies for biologics. We will also consider the patentability hurdles that formulation patents typically must overcome and we will consider case studies of both small molecule and biologic formulation patents to identify the best strategies for obtaining strong and defensible formulation patents.

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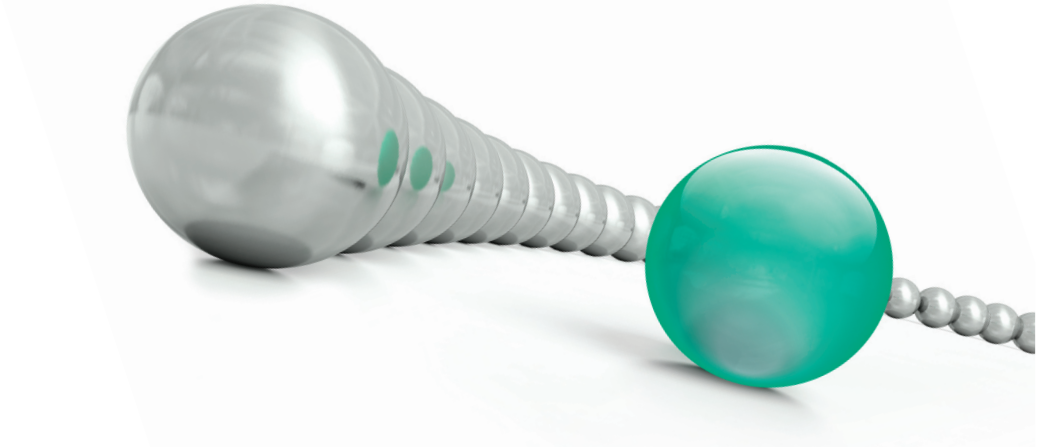

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Poster Abstract

Assessing an interaction parameter for bioformulation stability in a single measurement: exploiting concentration gradients from Taylor dispersion

Rachel Bott, Seyi Latunde-Dada, David Barker and Oksana I. Leszczyszyn

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The self-association characteristics of molecules in dilute solutions are thought to be good indicators of stability. One measure of the propensity for self-association is the diffusion interaction parameter (kD). In existing methodologies the determination of this parameter requires several measurements to be undertaken over a concentration series, but here we show how this can be achieved in a single, low volume measurement using Taylor Dispersion Analysis (TDA). TDA is a fast and simple method for determining the diffusion coefficients of molecules in solution, which is achieved by monitoring the dispersion of a small plug of solute as it travels through a microcapillary. Dispersion of the solute plug results in a concentration profile, from which the kD can be extracted by determining the solute's diffusion coefficients as a function of concentration. Here, we apply our method to solutions that display either positive or negative interaction parameters with resulting kD values in good agreement with those from Dynamic Light Scattering (DLS) measurements and literature values. In addition, we also demonstrate how the technique can be used to assess the stability of Lysozyme in a series of different buffers.

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Poster Abstract

An injectable solid formulation for peptide stability and delivery

Asme Boussahel

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Glide Pharmaceutical Technologies have developed a novel approach for peptide delivery: A patient-friendly device designed for the delivery of peptides and proteins in a solid form as an alternative to needle and syringe injection of liquid formulations. One of the advantages of this new technology is the ability to stabilise the peptide in a solid formulation for a prolonged period of time. In addition to the benefits of the SDI 1.2 device for users, formulating peptides in a solid form ensures long-term stability at room temperature. In this poster, we report on a case study of octreotide as a model peptide. We aimed to achieve four objectives when designing the reported formulation. First, design a solid dose that maintains the peptide stability for a prolonged period of time. Second, ensure that the resulting mechanical properties of the implant are adequate for penetrating the skin. Third, achieve a dissolution rate fast enough to ensure a quick dissolution of the solid dose once in the subcutaneous tissue. Finally, ensure that the resulting pharmacokinetic profile is bioequivalent to its liquid formulation. Our findings showed that the octreotide could be formulated into our proprietary formulations as a solid form, with a prolonged stability at 40˚C for three months, which suggests a room temperature stability of up to six months. Terminal sterilisation resulted in approximately 1% drop in purity with no marked difference between the formulations stored at 5˚C or 40˚C. Using the SDI 1.2 device, terminally sterilised octreotide implants produced using our large-scale process were used for a pre-clinical pharmacokinetic study. The monitoring of the octreotide blood level over eight hours showed that the resulting pharmacokinetic profile was bioequivalent to that produced by the competing injectable liquid formulation Sandostatin®.

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Poster Abstract

Evaluation of protein hydration by vapor sorption methods

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Considering that hydration is a major factor in the activity and selectivity of enzymes in organic solvents the water and sorption isotherms and surface wettability would provide fundamental information on the mechanism of the hydration of enzymes and proteins. Samples of an amorphous solid dispersion in a binder (PP) were treated to incorporate protein (PPZ) into the amorphous system. The water vapor sorption behavior of untreated and protein treated drug samples were investigated by means of Dynamic gravimetric Vapor Sorption (DVS). Surface wettability experiments were performed by Inverse Gas Chromatography (IGC). Water sorption results show moisture-induced crystallization for PP between 40 - 60% RH. This crystallization event is significantly reduced with the addition of protein, indicating that the protein acts as a stabilizer. At low water concentrations water molecules bound to specific water binding sites at the protein surface, but at higher water concentrations, the isotherms indicate that condensation occurs. The surface wettability as measured by IGC showed that the untreated sample doesn't show a change in specific surface energy but the dispersive surface energy increases with the humidity, consistent with irreversible phase change shown by the DVS results. For the treated sample, the specific surface energy (acid/base properties) changes with increasing RH up to 70% RH before decreasing at 80% RH. The adsorption isotherms and surface characterization by IGC SEA allow the determination of the water concentrations at which organic vapor would compete with water for adsorption on the protein.

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Poster Abstract

Highly stable bulk API powder using XstalBio's solvent precipitation technology

K. Geals, F. McNamee, K. Davidson and B.D. Moore

XstalBio Ltd., CIDS, University Avenue, Glasgow G12 8QQ

XstalBio's protein precipitation process has been used routinely to produce dry powder formulations of various proteins (mAbs, vaccines etc.) with very high levels of stability to temperature stress. Recent analysis of protein formulations has shown that these powders have excellent stability and even after 5+ years of storage under various conditions, > 98% monomer can be retained. Our proprietary PCMC technology is suitable for a range of proteins to produce free flowing powders suitable for various applications including bulk API storage or as a final therapeutic product for inhalation, high concentration subcutaneous injection etc. The inclusion of XstalBio's patented stabilising additives to the formulation can assist to further enhance this stability effect. Proteins can be very sensitive to temperature and humidity stress as an aqueous solution, so are generally frozen or freeze-dried for storage and to achieve a marketable shelf-life. The storage of bulk API for 5+ years as a powder without the need for expensive freezing or freeze drying whilst remaining stable and bioactive would be of massive benefit to the pharmaceutical industry for both animal and human health. XstalBio will present this data for a range of protein formulations and describe the possible applications of these highly stable powders and precipitation stabilising additives for bulk API storage and as therapeutic delivery options capable of disrupting the status quo.

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Poster Abstract

Taylor Dispersion Analysis for the characterization of mixtures and quantification of aggregates

Seyi Latunde-Dada, Rachel Bott and Oksana I. Leszczyszyn

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In this work, we explore the application of Taylor Dispersion Analysis (TDA) to the analysis of mixtures and quantification of aggregates without the need for separation. TDA is a fast and simple method for determining hydrodynamic radii and its coupling with microcapillaries reduces sample consumption to just tens of nanolitres per measurement. Using UV detection, small sample pulses are monitored as they transition across detection windows to produce temporally evolved concentration profiles, or Taylorgrams. The use of fitting models allows the Taylorgrams of mixtures to be deconvoluted; providing the hydrodynamic radii and relative proportions of the individual components. Here, we present data on two types of mixtures that mimic samples typically encountered in Biopharmaceutical research and show how they can be characterized by TDA. The first example concerns the characterization of samples that have undergone low levels of self-association; whereas the second example considers mixtures containing higher order aggregates.

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Poster Abstract

Biophysical interactions of flavonoids with free-standing and Hg supported lipid monolayers of DOPC

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Interactions of flavonoids with membranes are a cross disciplinary area that cover wide branches of science ranging from food science to physical chemistry. The current study aimed to compare the interactions of flavonoids (quercetin, kaempferol, tiliroside, rutin, naringenin, hesperetin, naringin, catechin) with membranes composed of dioleoyl phosphatidylcholine (DOPC) using; Langmuir monolayers at the air-water interface and phospholipid monolayers on mercury (Hg) surfaces. The investigated flavonoids exhibited different mechanisms of action and the following effects were observed in the presence of the studied compounds; (a) flavonol aglycones (quercetin and kaempferol) have produced more profound response than flavanones (naringenin and hesperetin) and catechin towards the membranes. (b) Amongst the glycosylated forms, tiliroside demonstrated much higher interactions compared to rutin and naringin. (c) Surface pressure-area isotherms of Langmuir films have shown the incorporation of quercetin and tiliroside into lipid monolayer by expanding the film towards higher molecular areas whereas no change was observed with rutin. (d) An important finding obtained from Langmuir monolayers was that quercetin revealed a membrane stabilizing activity. The membrane stabilization action may render quercetin a promising candidate not only for food industry as an emulsion and foam stabilizer molecule but also it may help in developing new formulations based on natural compounds for medicinal applications. The present experiments demonstrate for the first time a systematic investigation of flavonoid-membrane interactions using lipid monolayers. The findings confirm the hypothesis that the differences are highly dependent on the structural characteristics of flavonoids.

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Poster Abstract

Effect of humidity on physical properties of pharmaceutical solids

Majid Naderi[1], Manaswini Acharya[1], Jürgen Dienstmaier[1], Anett Kondor[1] and Daniel Burnett[2]

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The stability and structure of drugs are of paramount importance for drug delivery. Dynamic gravimetric vapour sorption instruments (DVS) have become the standard method for investigating the vapour sorption properties for dissolution, stability, storage as well as formulation of drugs, excipients, and packaging materials (adhesion-cohesion studies)[2]. In addition, Inverse Gas Chromatography Surface Energy Analyzer (IGC SEA) has been used to determine adhesion properties, describing the interaction between drug and carrier.
A comparison between work of adhesion and cohesion allows for a prediction of mixture stability and release properties. The DVS results show that the amorphous lactose takes up a significant amount of moisture below 60% RH as would be expected for a highly amorphous material, however above 60% RH there is a sharp loss in mass. Similar behaviour is observed for Tiotropium Bromide, which is typical of hydrate formation i.e. a large increase in water sorption capacity at a distinct RH. The shape of the resulting hysteresis gap between the sorption and desorption isotherms also supports the hydrate formation in both samples.
The IGC SEA profiles show that the samples are energetically heterogeneous, meaning the surface energy changes as a function of surface coverage. Works of adhesion and cohesion have been calculated as descriptive interaction parameters for each drug/excipient. The higher the work of adhesion the higher the drug-carrier interaction would be. A high work of adhesion relative to the work of cohesion also suggests a low segregation of the drug-excipients mixture. The influence of the humidity for these parameters was also investigated.

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Poster Abstract

Stabilisation of the membrane target: development of SRCD spectroscopy techniques for quantitative in vitro binding studies of membrane protein-ligand/drug interactions

Patching S.G.[1] Edara S.[1], Hughes C.S.[2], Siligardi G.[3], Hussain R.[3] & Phillips-Jones M.K.[2]

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Membrane proteins currently constitute approximately 60% of approved drug and biopharmaceutics targets. In a post-genomic era, the availability of genomic sequence information derived from a wide range of eukaryotic, eubacterial and archaean organisms reveals that 20-30% of open reading frames are predicted to encode integral membrane proteins, far more than anticipated, and suggesting that a wealth of membrane proteins are available to serve as new potential targets for the discovery of further modulatory biopharmaceutical drugs in the future. One bottleneck in in vitro studies of membrane protein-ligand/biopharmaceutical drug interactions is the availability of sufficient quantities of stable, purified intact membrane proteins (which are hydrophobic and technically-challenging). Here we describe methods suitable for the routine production of milligram quantities of a purified bacterial membrane sensor kinase protein FsrC and its stabilisation in detergent micelles. Initial studies to characterise FsrC interactions with its pheromone ligand GBAP using SRCD spectroscopy at the Diamond beamline B23 demonstrated that the membrane protein was in an unstable state as revealed through far-UV measurements of secondary structural conformation and α-helical content; spectra could not be reliably or consistently overlaid. Following trials of a variety of buffer and other conditions the protein was screened for stability using SRCD measurements. Conditions under which FsrC was stabilised were identified by confirming that there were no significant changes in the overlaid spectra during the time period of experiments. Stabilised FsrC was then used in SRCD spectroscopy measurements in the near-UV region to determine the binding affinity for the GBAP ligand; the k_d value was determined to be 2μM. Although CD methods have previously been used extensively to obtain qualitative data on membrane protein conformational changes induced upon ligand binding, this is the first report of its use to determine quantitative data on ligand binding by any membrane protein. Furthermore, we have shown that CD spectroscopy provides a valuable screening tool for confirming membrane protein stability prior to downstream biopharmaceutical testing or structural methods such as crystallisation and NMR experiments in which target stability is of paramount importance.

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Poster Abstract

Ion-specific interactions between Hofmeister salts and barnase: a mechanism to explain how Hofmeister salts modulate protein stability

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The effect three Hofmeister salts (Na_2SO_4, NaCl and NaSCN) had on the chemical shift values of amide, carbonyl, methylene and methyl groups on the protein Barnase was investigated using nuclear magnetic resonance (NMR) spectroscopy. This NMR work demonstrates that the anion and cation components of salts are capable of weakly binding with solvent exposed partial charges at low salt concentrations (<100 mM). This binding saturates at higher salt concentrations (>100 mM) and that additional salt components after this point primarily interact with the solvent. Previous differential scanning calorimetry (DSC) studies with different proteins have shown that low salt concentrations modulate protein thermal stability to a small degree which does not correlate with the salts Hofmeister effect. At higher concentrations the salts traditional Hofmeister effect on protein stability is observed; high charge density anions increase protein stability and low charge density anions decrease protein stability. From the NMR and DSC data it can be suggested that salts do not modulate protein stability by a significant amount when they bind to the protein surface. Instead they most likely affect stability through modulating the Gibbs free energy required to hydrate the newly exposed core of the unfolding protein. Similar protein stability effects have been previously observed with amino acids and osmolytes suggesting that they could also modulate protein stability by a similar mechanism. This work would be of great interest to individuals and companies working with protein formulations as it offers a potential mechanism to explain how excipients influence protein stability.

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Poster Abstract

The importance of measuring the second osmotic virial coefficient, B_{22} at a constant solvent chemical potential

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A better understanding of aggregation requires first determining the properties of partially folded states, which are believed to be key intermediates in the pathway. In this work we probe the interactions between partially folded states by using static light scattering to determine the second osmotic virial coefficient, B_{22} for solutions of lysozyme containing urea. Our initial findings indicate there is an apparent decrease in the measured molecular mass of lysozyme with increasing urea concentration. Since molecular weights less than monomer are not possible further investigation was warranted. Factors that could affect the measured molecular mass include the refractive index increment of the protein (dn/dc). In the rigorous thermodynamic analysis of light scattering for a multi-component solvent (i.e. excipient, salt, and water), the true molecular weight and B_{22} are measured when dn/dc is measured at constant solvent chemical potential. Since dn/dc from dialysis equilibrium could not be measured experimentally in the presence of urea, measurements were instead made for sucrose solutions, which also exhibit a decrease in average molecular mass as a function of sucrose concentration. Measurements of dn/dc at constant chemical potential as a function of sucrose concentration indicate the value decreases below the commonly used value of 0.185mL/g. In addition, when the correction is applied to the light scattering equation, the measured molecular weights are equal to or slightly above monomer. The correction also significantly impacts the trends observed in the measured B_{22} values for urea and sucrose solutions. In particular for sucrose solutions, without the correction, the B_{22} values appear to increase with increasing sucrose concentrations. However, after the corrections are applied the B_{22} values decrease with increasing excipient concentration. Corrected B_{22} values for both urea and sucrose, highlight the importance of measuring dn/dc instead of assuming the average value of 0.185mL/g is appropriate under any condition.

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Poster Abstract

Improving our products through the application and evolution of platform formulation

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Data generated from legacy protein molecules has shown that use of platform formulation is adequate to obtain the required shelf life to proceed quickly into FTIH studies which significantly reduces development cost and time. GSK generated sufficient stability data on lead candidates using the platform formulation. However, recent evidences suggest that the platform formulation may be unsuitable in some cases especially for a sub-class of proteins. One such molecule was a "typical" protein molecule which formed a highly viscous gel in the platform formulation. The mitigation of this viscosity issue could have taken two different paths- changing the design of the molecule to fit the platform buffer or developing a new formulation buffer to fit the molecule. The second approach was undertaken. Buffer screening and excipient screening carried out during the formulation development helped to determine the right conditions where the molecule would be stable. Thus the viscosity issue was successfully mitigated. GSK BioPharm portfolio is continuously increasing, however the platform formulation may not provide sufficient stability and shelf life. Hence, classical formulation development studies are performed for molecules that do not fit the platform formulation.

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Poster Abstract

Enabling convenient patient administration: application of a novel excipient to stabilise monoclonal antibody biotherapeutics at high concentrations

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With increasing competition in the biopharmaceutical market there is a strong trend toward improving convenience of administration. A switch from intravenous infusion to a convenient subcutaneous injection often requires an increase in protein concentration, leading to reduced stability and high viscosity, reducing shelf-life and causing injectability issues. This poster describes the protein stabilisation and viscosity reduction properties of novel excipient Triethylenetetramine (TETA). Nominal and high concentration (>100 mg/mL) monoclonal antibody (mAb) biotherapuetics were formulated using Arecor's proprietary Arestat™ protein stabilisation technology in the presence of TETA. These preparations were subjected to long-term temperature stress. Major protein degradation products and physico-chemical properties were evaluated to demonstrate the benefits of TETA. It demonstrated a significant stabilising effect, reducing protein aggregation and formation of visible particulates, minimising protein fragmentation and reducing viscosity by up to 52% when used in combination with the Arestat™ technology. Preliminary intravenous toxicology data using an in vivo rat model indicates an MTD of 100mg/kg/day, significantly above the effective level of TETA as an inactive ingredient. TETA demonstrates powerful stabilisation of nominal and high concentration preparations of biotherapeutic mAbs enabling the potential for new, convenient, administration formats that can significantly improve patient quality of life.

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Stability of biopharmaceuticals

From molecular interactions to successful products

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