



The Pfizer Institute for Pharmaceutical Materials Science



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What is it?

The Pfizer Institute for Pharmaceutical Materials Science is a research based collaboration between Pfizer Global R&D, the Cambridge Crystallographic Data Centre (CCDC) and two departments of the University of Cambridge: the Department of Materials Science and Metallurgy, and the Department of Chemistry.

Where is it?

The Institute is based within the University of Cambridge, having offices and laboratory space within our partner institutions.

Activities are co-ordinated from the Institute administration office within the Department of Materials Science & Metallurgy.

What does it do?

The Institute is a multidisciplinary partnership that seeks to draw upon the resources and expertise within several university departments and within the CCDC, and to combine these to generate a new perspective on our understanding of the properties of materials used in pharmaceutical products.

It embraces the two general approaches of computational modelling and experiment.

Modelling and Experimental

Running the Institute

The heart of the Institute is the 12 Post Doctoral Research Scientists and 9 Post Graduate Research students who are working on the project portfolio. They are supported directly by both academic supervisors from the University and the CCDC, and project supervisors from Pfizer Global R&D. The Institute's day to day work is assisted by three members of Assistant Staff.

The project portfolio is co-ordinated by two Scientific Implementation Panels both of which have representation from Pfizer and the University.

Responsibility for directing the science portfolio of the institute and its overall functioning resides with the Governing Board.

Directors

Professor Alan Windle	Director	pipmsdirector@msm.cam.ac.uk
Professor Bill Jones	Deputy Director	wj10@cam.ac.uk

Assistant Staff

Mrs Rebecca Pritchard	Administrator	pipmsadmin@msm.cam.ac.uk
Mr Chris Amey	Chemistry Technician	
Mr Wayne Hough	Materials Science Technician	

Governing Board

Dr Frank Allen	Executive Director, CCDC
Dr Tony Auffret	Pfizer Global Research and Development, Sandwich (Co-Chair)
Dr Ruth Cameron	Reader in Polymers and Medical Materials
Dr Robert Docherty	Pfizer Global Research and Development, Sandwich
Dr Keith Horspool	Pfizer Global Research and Development, Groton
Professor Bill Jones	Professor of Materials Chemistry
Professor Alan Windle	Professor of Materials Science (Co-Chair)

Secretariat

Mr Olivier Drap	Pfizer Global Research and Development
Dr Rachel Hobson	University of Cambridge, Industrial Liaison
Mrs Rebecca Pritchard	Board Secretary

Science Implementation Panel Chairs

Dr James Elliott	Experimental
Dr Jonathan Goodman	Modelling



Changing the way we work:

Putting Materials Science at the heart of pharmaceutical product development

The purpose of the Institute can be summarised in one phrase – “changing the way we work”.

Producing a safe and efficacious new medicine is a long and exacting process and the pharmaceutical industry strives to increase efficiency and productivity, establishing robust drug products that can be manufactured reliably and reproducibly. With production running at hundreds of thousands of tablets an hour, making sure each and every one is identical is not a trivial process. At the product design stage we must ensure that we identify the most suitable and stable form of the drug substance and develop a formulation and a manufacturing process that will stand up to the rigours of commercial scale operation.

Increasingly the industry is looking to new ways of working, involving small-scale predictive tests and *in silico* simulation.

The University of Cambridge and the CCDC have joined with Pfizer to add a dynamic new vigour to changing the way we work and to meet these new 21st century challenges.

Building a firm foundation:

The Pfizer Institute of Pharmaceutical Materials Science 2002 -2005

Following agreement between the partners in 2001, the Institute began its scientific work in 2002 with 14 scientists and 12 three-year projects initially divided into three strategic themes:

Structural and Chemical Properties

Mechanical Properties

Functional Properties

As the Institute developed further projects were added, additional scientists joined the Institute and a firm scientific foundation built. During this period Institute scientists published almost 50 papers in peer-reviewed journals.

This scientific work has added valuable contributions across a wide range of fields from computational simulation of amorphous materials to controlled crystallisation on surfaces, and from whole tablet internal imaging to the identification of a novel polymorph in bone formation.

In particular the work built four platforms for future development

Cocrystals: an alternative to salt formation for active pharmaceutical substances

Structural Informatics; a rational basis for identifying the most stable crystalline form of a drug.

Crystal Structure Prediction; *ab initio* prediction of pharmaceutical crystal structures.

Computational Powder Dynamics; the influence of particle properties on flow and compaction

These platforms are now being established in Pfizer's Global R&D operation.

Securing the future:



The Pfizer Institute for Pharmaceutical Materials Science 2005 - 2008

In 2005, the Institute embarked upon 15 new projects, building on the platform that had been established in 2002 – 2005 and addressing new challenges arising from Pfizer's emerging inhalation portfolio. Some of these newer projects are building a base to develop our understanding of the surface properties of pharmaceutical materials. In mid 2007, this involves more than 20 scientists actively engaged in scientific research.

List of Current projects

E = Experimental Project

M = Modelling Project

SOLID STATE INFORMATICS AND CRYSTAL STRUCTURE PREDICTION

P5	M	<i>Ab initio</i> crystal structure and property prediction
P13	E	Novel methods for the prediction of solubility
NP4a	E	Cocrystal design for non-polar (weak synthon) molecules
NP4b	E	Preparative methods for cocrystal screen development
NP5a	M	<i>Ab initio</i> predictive tools for salt structures
NP5b	M	<i>Ab initio</i> predictive tools for crystals containing flexible molecules
NP5c	M	Software and informatics development

COMPUTATIONAL POWDER DYNAMICS

NP6a	M	Predictive methods for powder flow and particle packing
NP6b	M	Effect of cohesive forces on flow of granulated particles
NP6c	M	Modelling of particle/particle interaction in micronised cohesive blends
NP6d	E	Effect of particle shape and size distribution on cohesive powder blend flow
NP7	M	Modelling the effects of compaction kinematics on tablet properties
NP8	E	Tablet pore structure, compaction kinetics and dissolution

PHARMACEUTICAL SURFACE SCIENCE

P14	E	Optimising the use of nanoindentation in pharmaceutical solid analysis
NP1a	E	Solid state chemistry and excipient incompatibility
NP1b	E	Spatially resolved characterisation of amorphous and crystalline materials
NP15a	E	Production of nanoparticles of pharmaceutically relevant materials
NP15b	E	Properties of nanoparticle ribbons
NP16	E	The transport of nanoscale particles across biological barriers



Making the Institute work: key people who run the Institute

The Pfizer Institute for Pharmaceutical Materials Science works because of the people who take care of the day-to-day business, administration, supervision, mentorship, guidance and governance. These people are:

Dr Frank Allen	<i>Executive Director, CCDC</i>
Dr Serena Best	<i>Reader in Ceramics and Medical Materials</i>
Dr Ruth Cameron	<i>Reader in Polymers and Medical Materials</i>
Dr Graeme Day	<i>Royal Society Fellow, Chemistry Dept</i>
Dr James Elliott	<i>University Lecturer</i>
Dr Laszlo Fabian	<i>Senior Research Associate, CCDC</i>
Prof Robert Glen	<i>Director, Unilever Centre for Molecular Sciences Informatics</i>
Dr Jonathan Goodman	<i>Unilever Centre for Molecular Sciences Informatics</i>
Prof Bill Jones	<i>Professor of Materials Chemistry and Head of the Chemistry Department</i>
Dr John Mitchell	<i>Unilever Centre for Molecular Sciences Informatics</i>
Prof Alan Windle	<i>Professor of Materials Science</i>

Scientific Work at the Institute:

SOLID STATE INFORMATICS AND CRYSTAL STRUCTURE PREDICTION



AB INITIO CRYSTAL STRUCTURE AND PROPERTY PREDICTION

PhD Student: Miss Aurora Cruz-Cabeza

Principal Investigator: Professor Bill Jones

Pfizer Supervisor: Dr Neil Feeder

There is an increasingly strong driving force to predict the properties of a drug in its solid form and this, in turn, drives the need to predict three-dimensional structure. We have refined commercially available predictive packages with the introduction of novel search algorithms, especially in the area of H-bonding pattern analysis. We are now applying these models to the prediction of novel polymorphs and solvates.

NOVEL METHODS FOR THE PREDICTION OF SOLUBILITY

PhD Student: Mr David Palmer

Research Associate: Dr Toni Llinas Marti

Principal Investigator: Dr Jonathan Goodman

Pfizer Supervisor: Dr Iñaki Morao

Improving the prediction of solubility is essential to reducing the current unacceptable attrition rate in drug development. We have generated a conceptually transparent method for the prediction of energy-related molecular properties based on an automated, but chemically rich, atom typing scheme. To support this we are experimentally measuring a comprehensive set of solubility parameters for drug-like molecules under standard conditions. This will allow us to develop the methodology for the prediction of solubility for drug like molecules with particular reference to its dependence on pH, salt effects and polymorphism.

COCRYSTAL DESIGN FOR NON-POLAR (WEAK SYNTHON) MOLECULES

Research Associate: Dr Tomislav Friščič

Principal Investigator: Professor Bill Jones

Pfizer Supervisor: Dr Pete Marshall

In traditional pharmaceutical development the formation of salts offers a route to solid forms that are more stable than crystallisation of a neutral form of the drug substance. With weak and non-polar molecules salt formation is not appropriate but cocrystal formation can extend the range of stable solid forms accessible for development. In the current state of the art the selection of cocrystal partner synthons is somewhat arbitrary and the development of rational selection of partner synthons for screening strategies is needed.

PREPARATIVE METHODS FOR COCRYSTAL SCREEN DEVELOPMENT

Research Associate: Mr Shyam Karki

Principal Investigator: Professor Bill Jones

Pfizer Supervisor: Dr Pete Marshall

Some methods of cocrystal formation e.g. grinding appear to be superior to solution based methods, but are not particularly suited either to automated screening methods or large scale chemical manufacture. Although solution based methods are more attractive for screening and scale up, there is an overriding need to develop routine methods for cocrystal formation. The project could explore either solvent selection strategies for cocrystal formation or investigate alternate scalable methods of synthesis and manufacture.

PREDICTIVE TOOLS FOR SALT STRUCTURES

PhD Student: Miss Katarzyna Hejczyk
Principal Investigator: Dr Graeme Day
Pfizer Supervisor: Dr Neil Feeder

Ab initio based methods are becoming standard tools in the search for and identification of stable polymorphic forms of drug crystals suitable for pharmaceutical development. Building upon the successes and experience developed in PIPMS Phase I for single component crystals and solvates of small rigid molecules, we now wish to extend these studies to areas where traditional methods are untested or weak. This project aims to develop modelling methods for the prediction of salt structures.

PREDICTIVE TOOLS FOR CRYSTALS CONTAINING FLEXIBLE MOLECULES

Research Associate: Dr Tim Cooper
Principal Investigator: Dr Graeme Day
Pfizer Supervisor: Dr Neil Feeder

Crystal structure prediction methods are becoming reliable for small rigid organic molecules, but there are important difficulties in extending current methods to flexible molecules. We are developing modelling methods to overcome these difficulties and allow reliable predictions of the stable structural forms of larger, flexible molecules.

INFORMATICS SOFTWARE DEVELOPMENT

Research Associate: Dr Peter Galek
Principal Investigator: Dr Frank Allen
Pfizer Supervisor: Dr Neil Feeder

In Phase I of the Institute, progress in *ab initio* and informatics-based solid form selection benefited greatly from a close and facilitated interaction involving project research scientists and software development for structural search and data analysis using the Cambridge Structural Database. This CCDC based support and development continues throughout Phase II.

INFORMATICS APPLICATIONS

Research Associate: Dr Laszlo Fabian
Principal Investigator: Dr Frank Allen
Pfizer Supervisor: Dr Neil Feeder

Knowledge of the systematics of existing crystal structures is vital in predicting the most probable patterns of hydrogen bonds and other non-bonded interactions that are likely to create novel solid forms, e.g. cocrystals, polymorphs, etc. Such knowledge has predictive ability in its own right, and is a valuable adjunct to *ab initio* computational approaches to crystal structure prediction.



PREDICTIVE METHODS FOR POWDER FLOW AND PARTICLE PACKING

PhD Student: Miss Kimberley St John-Green
Principal Investigator: Dr James Elliott
Pfizer Supervisor: Dr Craig Bentham

The Phase I model can be refined to address two emerging needs. Firstly, we need to address the growing use of cohesive drug substance forms in standard tablet formulations, and to predict the behaviour of such materials. The second is the growing use of small scale tests that are predictive of behaviour at larger scales of operation. Tablets are typically produced by the compaction of granulated materials, rather than the direct compression of powder blends as powder flow, in large scale operations, can be difficult to predict or control. We need to correlate the parameters measurable in small scale tests to predicted and real behaviour at scale.

EFFECT OF COHESIVE FORCES ON FLOW OF GRANULATED PARTICLES

Research Associate: Dr Meenakshi Dutt
Principal Investigator: Dr James Elliott
Pfizer Supervisor: Dr Bruno Hancock

Pharmaceutical materials blends are typically densified by granulation and the granules compressed into tablets. Historically, the majority of drug substances have properties that lead to non-cohesive granules. There is, however, a growing use of cohesive drug solid forms and a consequential growing need to model this behaviour.

MODELLING OF PARTICLE/PARTICLE INTERACTION IN MICRONISED NON-COMPRESSED COHESIVE BLENDS

Research Associate: Dr Yuen Sin Cheong
Principal Investigator: Dr Serena Best
Pfizer Supervisor: Dr Imogen Gill

Powder formulations for inhalation usually consist of small drug particles bound to the surface of carrier particles, which are then aerosolized and separate during delivery in a complex process that depends on the gas flow rate, shear forces, temperature and humidity in the system. This project aims to understand the fundamental behaviour of inhaled powders by developing approaches to characterize flowability and the effect of interparticle forces from an experimental and modelling perspective.

EFFECT OF PARTICLE SHAPE AND SIZE DISTRIBUTION ON COHESIVE POWDER BLEND FLOW

PhD Student: Mr Christopher Watling
Principal Investigator: Dr Ruth Cameron
Pfizer Supervisor: Dr Valerie Diart

This project relates to formulations used in inhalation-based therapies. Typically these consist of a micronised drug substance and an inert lactose carrier. Micronisation results in drug substance particles, typically 3-5 µm and of a highly cohesive nature. During formulation manufacture and device filling we require the drug substance to adhere homogeneously throughout the bulk of carrier material, but, as larger carrier particles are excluded from the lung, on inspiration the drug substance must segregate from the carrier. This project is intended to study the behaviour of inhalation formulations as a function of particle properties, shape and size.



MODELLING THE EFFECTS OF COMPACTION KINEMATICS ON TABLET PROPERTIES

Research Associate: Dr Lianghao Han

Principal Investigator: Dr James Elliott

Pfizer Supervisor: Dr Hussein Mohammed

During Phase I of the Institute we have developed a model that predicts the stresses and some mechanical failure modes of tableted granules. This project extends that work to investigate the motions of the particles (kinematics) in the process of tablet formation from granulated materials.



TABLET PORE STRUCTURE, COMPACTION KINETICS AND DISSOLUTION

Research Associate: Dr Peter Laity

Principal Investigator: Dr Ruth Cameron

Pfizer Supervisor: Dr John Heimlich

One of the aims of the Institute has been to develop models of dosage form behaviour starting at molecular interactions in solid form selection, through the tableting process and ending with drug release. In Phase I of the Institute, we developed technologies to image pore structures in tablets. This project is exploring the link between tablet structure and performance.

PHARMACEUTICAL SURFACE SCIENCE

THE USE OF NANOINDENTATION IN PHARMACEUTICAL SOLID ANALYSIS

PhD Student: Miss Yousun Ha

Principal Investigator: Dr Serena Best

Pfizer Supervisor: Dr Lisa Taylor

The use of nanoindentation to measure physical properties that are key to predicting breakage behaviour during milling is becoming increasingly established within the pharmaceutical industry. The methodology, however, has been developed in other industries, e.g. ceramics. The effects of technique variables and the application of standard mathematical models to pharmaceutical materials has not been rigorously analysed. This project will develop a rational standard method for pharmaceutical materials.

SOLID STATE CHEMISTRY AND EXCIPIENT INCOMPATIBILITY

Research Associate: Mr Andrew Cassidy

Principal Investigator: Professor Bill Jones

Pfizer Supervisor: Dr Evgenyi Shalaev

At a simplistic level, two non-volatile, phase separated (crystalline) materials cannot interact chemically. Therefore excipient incompatibility should not occur with standard tablets. The fact that it does tells us that the unit operations of manufacture (most likely compaction and compression) alter this idealised situation. The hypothesis is that chemical reactions between drug and excipient are facilitated through the production of disordered, or amorphous regions, possibly solid solutions, of crystals or particles when they are subjected to compaction or compression.

SPATIALLY RESOLVED CHARACTERISATION OF AMORPHOUS AND CRYSTALLINE REGIONS

Research Associate: Dr Catherine Gardner

Principal Investigator: Professor Bill Jones

Pfizer Supervisor: Mr Barry Aldous

High energy milling is thought to induce disorder of the surface of a crystal, and in the field of inhalation formulation development, much effort is given to the characterisation of the “amorphous content” of micronised materials. Most standard tests (e.g. calorimetry) measure the total, bulk amorphous content, yet the behaviour of a micronised blend relates to particle interactions mediated by surface interactions. Spatially resolved characterisation that measures the surface component is required to understand the effects of disorder in particle interactions.

PRODUCTION OF NANOPARTICLES OF PHARMACEUTICALLY RELEVANT MATERIALS

Research Associate: Dr Jacqui Capes

Principal Investigator: Professor Alan Windle

Pfizer Supervisor: Dr Stefan Taylor

Nanoparticles, by virtue of their smallness, often show different properties, thermodynamically as well as kinetically, and as a result create pharmaceutical opportunities. The project is aimed at the creation of coatings based on oligomeric peptides of predetermined sequence, which will define nanoparticles of pharmaceutically relevant materials. While the coatings will initially be engineered to be soluble and bio inactive their promotion to a smart role is a mid-term objective.

PROPERTIES OF NANOPARTICLE RIBBONS

PhD Student: Mr Patrick Kiley

Principal Investigator: Professor Alan Windle

Pfizer Supervisor: Dr Stefan Taylor

This project seeks to develop methods for the directed assembly of nanometer sized particles of pharmaceutical materials. Although there are clear applications in the development of nanoparticulate medicines, one of the prime objectives of this project is to develop nanoparticles as models of particle surfaces. In micrometer sized particle, although interactions are mediated via surface contacts, the surface itself typically represents less than a fraction of 1% of the total material. With nanoscale particles, however, the ratio of surface to bulk molecules is sufficiently high that meaningful measurement can be made of surface properties. Such measurement will find particular application in understanding the behaviour of micronised inhalation medications, and will also impact significantly upon our ability to predict and control particle interactions in standard powder blending and granule compression operations in tablet manufacture.

THE TRANSPORT OF NANOSCALE PARTICLES ACROSS BIOLOGICAL BARRIERS

PhD Student: Dr Bijal Trivedi

Principal Investigator: Professor Alan Windle

Dr Steve Hladky

Pfizer Supervisor: Dr Tony Auffret

The transport of functionalized nanoparticles across the blood-brain barrier is a joint project between the nanotechnology laboratory in Materials Science and the pharmacokinetics laboratory in the Department of Pharmacology. It will study the influence of the size, shape and surface chemistry of nanoscale particles on their kinetics across the blood-brain barrier of a porcine model.

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