



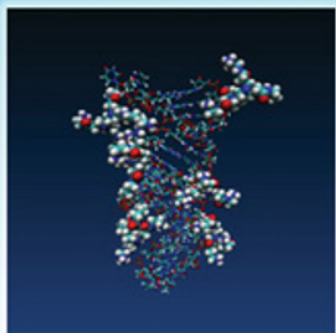
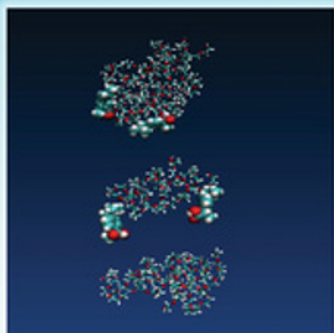
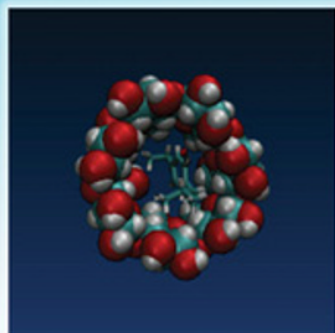
Editors

Defang Ouyang

Sean C. Smith

Computational Pharmaceutics

Application of Molecular
Modeling in Drug Delivery



Computational Pharmaceutics

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Computational Pharmaceutics

**Application of Molecular Modeling
in Drug Delivery**

Edited by

DEFANG OUYANG AND SEAN C. SMITH

WILEY

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Series Preface

The series *Advances in Pharmaceutical Technology* covers the principles, methods, and technologies that the pharmaceutical industry use to turn a candidate molecule or new chemical entity into a final drug form and hence a new medicine. The series will explore means of optimizing the therapeutic performance of a drug molecule by designing and manufacturing the best and most innovative of new formulations. The processes associated with the testing of new drugs, the key steps involved in the clinical trials process, and the most recent approaches utilized in the manufacture of new medicinal products will all be reported. The focus of the series will very much be on new and emerging technologies and the latest methods used in the drug development process.

The topics covered by the series include:

- *Formulation*: the manufacture of tablets in all forms (caplets, dispersible, fast-melting) will be described, as will capsules, suppositories, solutions, suspensions and emulsions, aerosols and sprays, injections, powders, ointments and creams, sustained release, and the latest transdermal products. The developments in engineering associated with fluid, powder and solids handling, solubility enhancement, and colloidal systems including the stability of emulsions and suspensions will also be reported within the series. The influence of formulation design on the bioavailability of a drug will be discussed and the importance of formulation with respect to the development of an optimal final new medicinal product will be clearly illustrated.
- *Drug delivery*: The use of various excipients and their role in drug delivery will be reviewed. Amongst the topics to be reported and discussed will be a critical appraisal of the current range of modified-release dosage forms currently in use and also those under development. The design and mechanism(s) of controlled release systems, including macromolecular drug delivery, microparticulate controlled drug delivery, the delivery of biopharmaceuticals, delivery vehicles created for gastro-intestinal tract targeted delivery, transdermal delivery, and systems designed specifically for drug delivery to the lung will all be reviewed and critically appraised. Further site-specific systems used for the delivery of drugs across the blood–brain barrier will be reported, including dendrimers, hydrogels, and new innovative biomaterials.
- *Manufacturing*: The key elements of the manufacturing steps involved in the production of new medicines will be explored in this series. The importance of crystallization; batch and continuous processing, seeding; mixing including a description of the key engineering principles relevant to the manufacture of new medicines will all be reviewed and reported. The fundamental processes of quality control including good laboratory practice (GLP), good manufacturing practice (GMP), quality by design (QbD), the Deming cycle, regulatory requirements, and the design of appropriate robust statistical sampling procedures for the control of raw materials will all be an integral part of this book series.

An evaluation of the current analytical methods used to determine drug stability, the quantitative identification of impurities, contaminants, and adulterants in pharmaceutical materials will be described as will the production of therapeutic biomacromolecules, bacteria, viruses, yeasts, moulds, prions, and toxins through chemical synthesis and emerging synthetic/molecular biology techniques. The importance of packaging including the compatibility of materials in contact with drug products and their barrier properties will also be explored.

Advances in Pharmaceutical Technology is intended as a comprehensive one stop shop for those interested in the development and manufacture of new medicines. The series will appeal to those working in the pharmaceutical and related industries, both large and small, and will also be valuable to those who are studying and learning about the drug development process and the translation of those drugs into new life-saving and life-enriching medicines.

Dennis Douroumis
Alfred Fahr
Juergen Siepmann
Martin Snowden
Vladimir Torchilin

Preface

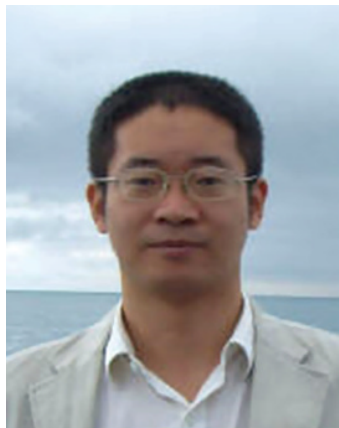
While computer-aided drug design (or rational drug design) has been practised for half a century, the application of computational modeling to drug delivery and pharmaceutical formulations “computational pharmaceutics” has emerged only in recent years. In combination with existing branches of pharmaceutics, it offers rapidly growing potential for developing rational, deductive, and knowledge-based strategies in pharmaceutics. Thus, this discipline has emerged and grown enormously in importance. Exploiting the exponential growth in power of high performance computing systems, computational pharmaceutics has the ability to provide multiscale lenses to pharmaceutical scientists, revealing mechanistic details ranging across chemical reactions, small drug molecules, proteins, nucleic acids, nanoparticles, and powders to the human body.

Given the advances in the field, it is becoming increasingly important that pharmaceutical scientists have cognizance of computational modeling, which may be anticipated to become a more common part of postgraduate curricula. While the fundamental theories and technical implementations of many of the methods in this book are complex, the computational software is becoming much more readily accessible and usable. Hence, it is no longer a prerequisite to understand in detail how the methods work at the theory and computer coding levels in order to gain substantial insights and benefits from carrying out simulations. Written for an audience with little experience in molecular modeling, with a focus on applications, this book will prove an excellent resource for researchers and students working in pharmaceutical sciences. We anticipate it will be useful not only for pharmaceutical scientists but more broadly for computational chemists looking to move into the pharmaceutical domain, for those working in medicinal chemistry, materials science, and nanotechnology.

Defang Ouyang
Sean C. Smith
March 2015

Editors' Biographies

Defang Ouyang



Dr Defang Ouyang is an Assistant Professor in the University of Macau, China. He has a multidisciplinary background in pharmaceutics and computer modeling, with experience in academia and industry. He completed his PhD in pharmacy at The University of Queensland, Australia, in 2010 and progressed directly to a faculty position at Aston University, UK in January 2011. At the end of 2014, he moved to the University of Macau. Since 2011, he has pioneered the integration of molecular modeling techniques and experimental approaches in the field of drug delivery – “computational pharmaceutics”. He has published over 20 refereed journal papers in this area. He chaired the Computational Pharmaceutics Workshop at the 2014 Controlled Release Society Annual

Meeting (Chicago, USA). Currently he supervises one PhD student and two MSc students. He has also successfully supervised one PhD student and 18 Master research projects.

Sean C. Smith



Professor Sean C. Smith received his PhD in theoretical chemistry at the University of Canterbury, New Zealand, in 1989. Following an Alexander von Humboldt Fellowship at the University of Göttingen, Germany and postdoctoral research at the University of California, Berkeley, USA he accepted a faculty position at The University of Queensland (UQ), Australia in 1993. He became Professor and Founding Director of the UQ Centre for Computational Molecular Science in 2002 and in 2006 his laboratory moved to the Australian Institute for Bioengineering and Nanotechnology at UQ. He was a founding chief investigator, computational program leader, and

Deputy Director in the Australian Research Council Center of Excellence for Functional Nanomaterials 2002–2010. In 2011, he undertook the role of Director of the Department of Energy funded Center for Nanophase Materials Sciences (CNMS) at Oak Ridge National Laboratory, USA. In 2014 he moved to the University of New South Wales (UNSW)

Australia as Professor of Computational Nanomaterials Science and Engineering and Foundation Director of the Integrated Materials Design Centre. His specific research involves theoretical and computational studies of structure, reactivity and catalysis, photochemistry, electrochemistry and transport phenomena within nanomaterials, proteins, and hybrid nano-bio systems as well as his long-time passions of chemical kinetics and reaction dynamics. He has published over 230 refereed journal papers. In 2006 he was recipient of a Bessel Research Award from the Alexander von Humboldt Foundation in Germany and in 2012 he was elected Fellow of the American Association for the Advancement of Science (AAAS).

1

Introduction to Computational Pharmaceutics

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1.1 What Is Computational Pharmaceutics?

It is a given that active pharmaceutical ingredients (APIs) should be made into safe and effective dosage forms or formulations before administration to patients. Pharmaceutics is the discipline to make an API into the proper dosage form or medicine, which may then be safely and effectively used by patients [1]. Pharmaceutics also relates to the absorption, distribution, metabolism, and excretion of medicines in the body. Branches of pharmaceutics include formulation development, pharmaceutical manufacture and associated technologies, dispersing pharmacy, physical pharmacy, pharmacokinetics, and biopharmaceutics [1–4]. Today there are various dosage forms, such as tablets, capsules, solutions, suspensions, creams, inhalations, patches, and recently nanomedicines (e.g., liposomes, nanoparticles, nanopatches). Although numerous new techniques have been developed for the form of dosage, current development of drug formulations still strongly relies on personal experience of pharmaceutical scientists by trial and error in the laboratory [1]. The process of formulation development is laborious, time-consuming, and costly. Therefore, the simplification of formulation development becomes more and more important in pharmaceutical research. *Computational pharmaceutics* involves the application of computational modeling to drug delivery and pharmaceutical

nanotechnology. In combination with existing branches of pharmaceuticals, it offers rapidly growing potential for developing rational, deductive and knowledge-based strategies in pharmaceuticals.

With stunningly rapid advances in hardware, theory and software algorithms, computer simulation is now able to model complex systems, which may be difficult, costly, or even impractical to measure or monitor directly by experiment [5, 6]. The first example of computer modeling was the simulation of the nuclear bomb process in the Manhattan Project, World War II. With the development of high performance computing, multiscale modeling techniques have been widely pursued, from quantum mechanics (QM) and molecular dynamics (MDs) to stochastic Monte Carlo methods, coarse grained dynamics, discrete element methods (DEMs), finite element methods as well as advanced analytical modeling. In principle, all properties of all systems are able to be described by QM. However, first principle calculations are limited to small systems, <1000 atoms, which is impractical for solving applications of large molecules or systems [5, 6]. MD simulations mimic the physical motion of atoms and molecules under Newton's laws of physics, which is applicable to larger systems containing millions of atoms [5, 6]. MD simulation is based on molecular mechanics, which models the interactions between atoms with force fields. Monte Carlo (MC) simulation uses the same empirical force field as MD simulation. However, MC simulation features playing and recording the results in casino-like conditions by repeated random sampling [5, 6]. Thus, unlike MD simulation, MC simulation cannot offer dynamical information with time evolution of the system in a form suitable for viewing. MC methods are especially useful for modeling systems with significant uncertainty and high degrees of freedom, such as polymer chains and protein membranes. For much larger systems, coarse-grain models do further classical approximations by treating functional groups as rigid bodies of constrained particles [5, 6]. The DEM is one of the numerical methods for computing the motion and effect of a large number of small particles, which is widely used in the pharmaceutical process and manufacturing [5, 6].

In the past three decades, the application of computational modeling approaches in the field of drug design (e.g., QSAR, ligand docking) has been intensively developed to the point of being a mature field [7]. Pharmaceutical research is, however, a far broader field than drug design alone. Proceeding beyond drug design, the application of computational modeling to drug delivery and pharmaceutical nanotechnology, *computational pharmaceutics*, is a very new field with great potential for growth [8]. As shown in Figure 1.1, computational pharmaceutics has the ability to provide multiscale lenses to pharmaceutical scientists, revealing mechanistic details ranging across the chemical reactions of small drug molecules, proteins, nucleic acids, nanoparticles, and powders with the human body. The aim of this book is to provide a contemporary overview of the application of computational modeling techniques to problems relating to pharmaceuticals (drug delivery and formulation development) that will be of great relevance for pharmaceutical scientists and computational chemists in both industry and academia. Contributions from leading researchers cover both computational modeling methodologies and various examples where these methods have been applied successfully in this field.

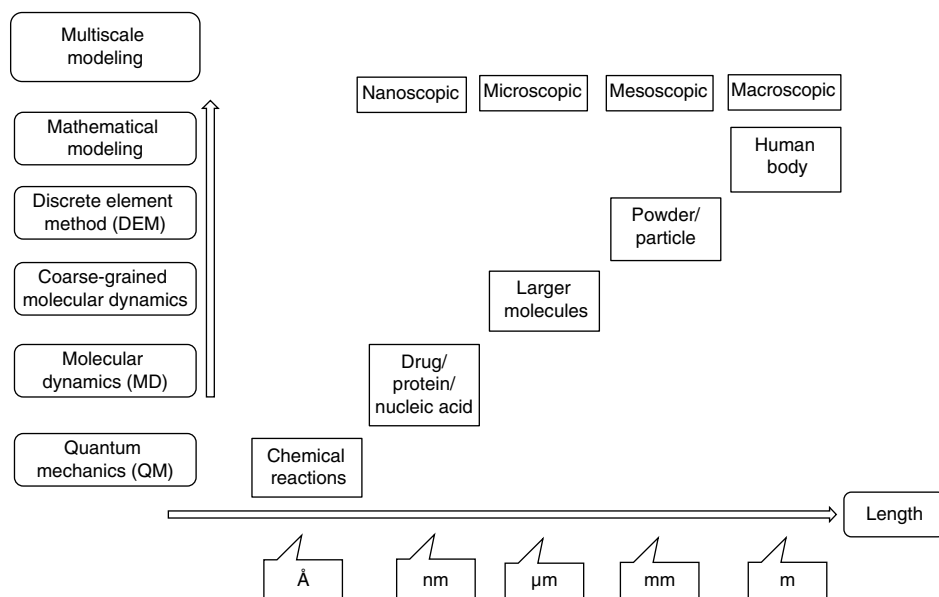


Figure 1.1 Application of computational pharmaceutics.

1.2 Application of Computational Pharmaceutics

Polymorphism of small drug molecules (e.g., crystal, hydrate, solvate, salt, cocrystal) plays a very important role in pharmaceutical research because it greatly influences the dissolution behavior and the bioavailability of pharmaceutical products. Thus, crystal structure prediction (CSP) methods have gained wide attention from pharmaceutical scientists. Chapter 2 discusses the general principles of CSP and recent progress in solid form screening by the crystal energy landscape method.

Cyclodextrins are a family of cyclic oligosaccharides, which are widely used in drug delivery and formulations for the solubilization of poorly soluble drugs. In Chapter 3, the physicochemical principles of cyclodextrin/drug complexation, experimental characterization and recent theoretical progress of drug/cyclodextrin modeling are discussed.

Polymeric-based micellar vehicles have been widely used in pharmaceutics for the delivery of both hydrophilic and lipophilic drugs. Multiscale modeling for polymeric-based vehicles for drug delivery is discussed in Chapter 4, including different computational approaches, micellar self-assembly and stability, the interaction of Taxol with model cellular membranes, and Taxol–tubulin association.

Solid dispersion refers to the dispersion of drug molecules in carriers in a solid state, prepared by the hot melting method. Poor physical stability has strongly hindered the commercialization of this technique. Chapter 5 discusses the possible molecular structure of amorphous solid dispersions and the mechanism of physical stability of this technology.

Biological lipid membranes are the key to drug absorption and bioavailability. Liposomes, artificially prepared vesicles with a phospholipid bilayer, are widely employed in drug

delivery for cancer and other diseases. Chapter 6 reviews the theoretical progress of lipid membrane models, small-molecular uptake and permeation across lipid membranes, nanoparticle–membrane interaction, and the mechanism of chemical penetration enhancers.

Protein/peptide drugs are becoming increasingly important in the pharmaceutical market. However, the development of stable and effective formulations for biopharmaceuticals is still quite challenging for pharmaceutical scientists. Chapter 7 summarizes the diverse modeling results on the solution behavior of protein formulation, including protein aggregation pathways in liquid formulations, protein–cosolvent interactions, and protein–protein interactions.

Inorganic nanoparticles had been increasingly utilized for drug/gene delivery in recent decades. One of the main advantages of nanoparticle drug delivery systems is the targeting effect to specific organs and tissues. Chapter 8 discusses recent progress in computational modeling of inorganic nanoparticle drug delivery systems: carbon nanotubes, graphene/graphene oxide, silica, and gold nanoparticles.

Although the concept of nanodiamonds (diamond nanoparticles) for drug delivery is still in its infancy, recently nanodiamonds have been widely studied for bio-imaging and drug targeting for improved chemotherapeutic effect. Chapter 9 reviews the structure of the individual nanodiamond, its surface chemistry and interactions, and nanodiamond drug delivery systems.

Layered double hydroxides (LDHs) are composed of nanoscale cationic brucite-like layers and exchangeable interlayer anions. LDH nanoparticles are an efficient drug delivery system for anionic chemicals, such as small drug molecules (e.g., methotrexate, heparin) and nucleic acids (RNA and DNA). In Chapter 10, different computational approaches are discussed to investigate the properties and interactions of LDH/anion systems.

The structure of particles or powders plays an important role in many dosage forms, such as tablets, granules, and capsules. However, the microstructure of these dosage forms is less well investigated. Chapter 11 reviews the principles of synchrotron radiation-based microtomography (SR- μ CT) and its application to determine the particulate architecture of granules, osmotic pump tablets, and HPMC matrix tablets.

Physiology-based pharmacokinetics plays an important role in pre-clinical drug development and formulation development. Chapter 12 discusses the principles of pharmacokinetic modeling and simulation and commercially available models for pharmaceutical scientists.

1.3 Future Prospects

“Today the computer is just as important a tool for chemists as the test tube” (Karplus, Levitt, and Warshel, Nobel Prize in Chemistry 2013). Analogous to the paradigm shift of drug development in the past three decades by computer-aided drug design, computational pharmaceutics also has great potential to shift the paradigm of drug delivery research in the near future [8].

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2

Crystal Energy Landscapes for Aiding Crystal Form Selection

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2.1 Introduction

The fundamental interrelationships between crystal structure, properties, performance and processing of a drug form the basis of “turning the development of pharmaceutical products from an art into a science” [1]. Thus, the development of an active pharmaceutical ingredient (API) into a pharmaceutical product requires detailed knowledge of its solid state forms and their physical properties. Even if the drug is not going to be delivered in a solid tablet, for example from a transdermal patch, there is a need to avoid crystallisation in the product. The manufacturing process will usually involve crystallisation as a purification step, possibly for separating out enantiomers as well as less similar synthetic impurities. Hence the design of the manufacturing process requires information about the solid forms that could be involved, including any hydrates or solvates [2].

An API rarely has only one crystalline phase. There may be polymorphs, hydrates, solvates, salts or cocrystals, though only cases where the solvent, counterion or cofomer is pharmaceutically acceptable can be considered for development into a drug product. Salts and cocrystal forms can be used to improve solubility and dissolution rate [3]. Hence, a careful consideration of all alternatives is needed to select the physical form that will be used in the product, and the stability of multicomponent crystalline forms relative to their components is a key property [4].

Polymorphism [5, 6], the ability of a molecule (or defined stoichiometry hydrate, salt or cocrystal) to adopt more than one crystal structure, plays an important role in pharmaceutical development, because the physical properties of a crystal, most critically the solubility and dissolution rates, can differ between polymorphs. Thus, the pharmaceutical product must contain just the approved polymorphic form. A drug is most often formulated using the most stable polymorph to avoid potential problems of phase transformations during storage. However, since metastable polymorphs or even amorphous forms may have better properties, particularly being more soluble, a metastable form may be developed provided that transformation to the more stable form during production and storage can be excluded. Unfortunately, molecules do not necessarily readily crystallise in their most stable form: indeed Ostwald's Rule of Stages [7] encapsulates the observation that metastable forms tend to be the first observed. The problem is that, once a more stable form has been nucleated, it can prove very difficult if not practically impossible to produce the metastable crystal structure, giving rise to the phenomenon of disappearing polymorphs [8]. There was a huge expansion of industrial and academic research into organic polymorphism after the Norvir[®] crisis, when Abbott Laboratories had to reformulate ritonavir at considerable expense after a novel, thermodynamically more stable, considerably less soluble polymorph emerged two years after the launch [9]. This led to the development of many solid form screening and characterisation methods [10]. However, polymorphism still causes problems within the industry, such as the crystallisation of rotigotine within the transdermal patches being used to deliver it to sufferers of Parkinson's disease in 2008 [11]. How can you ensure experimentally that the most stable crystalline form is known? One rare example of knowing that the most stable form has not yet been crystallised has been reported for a melatonin agonist, because the inactive enantiomer has two polymorphs and despite extensive efforts only the corresponding metastable form can be found for the active enantiomer [12]. The rationalisation is that the inactive enantiomer has come into contact with a chiral substance or surface capable of nucleating its most stable polymorph. It is the uncertainty in knowing that the most stable form has been crystallised that led to considerable practical interest in developing a computational method of predicting the most stable crystal structure of a given API [4].

Crystal structure prediction (CSP) methods gained their name decades ago, when people were trying to predict the crystal structure of a molecule, assuming that polymorphism was unlikely. The challenge was to predict the crystal structure of a molecule from just the chemical diagram. Success would indicate that all the factors which determined which crystal structure was adopted had been incorporated into the model. Most methods assumed that this involved searching for the most thermodynamically stable crystal structure, assuming that thermodynamics was the major determinant. The hope behind the first CSP programs was that there would be a significant energy difference between the observed structures and the hypothetical structures generated, a hope that was quickly dashed [13, 14]. The growing realisation that the prediction of crystal structures was industrially relevant, as well as being a fundamental scientific challenge, led to the Cambridge Crystallographic Data Centre organising blind tests of CSP [15–19]. In these tests, groups developing CSP methods are sent the chemical diagrams of the molecules whose solved crystal structures are kept confidential until the groups have submitted three predictions by a deadline. The accounts of the discussion of the results form an excellent review of both the variety of methodologies and the progress in the field, as well as showing the low success rate (Figure 2.1). In the fourth blind test (CSP2007), one group had the remarkable success of correctly predicting

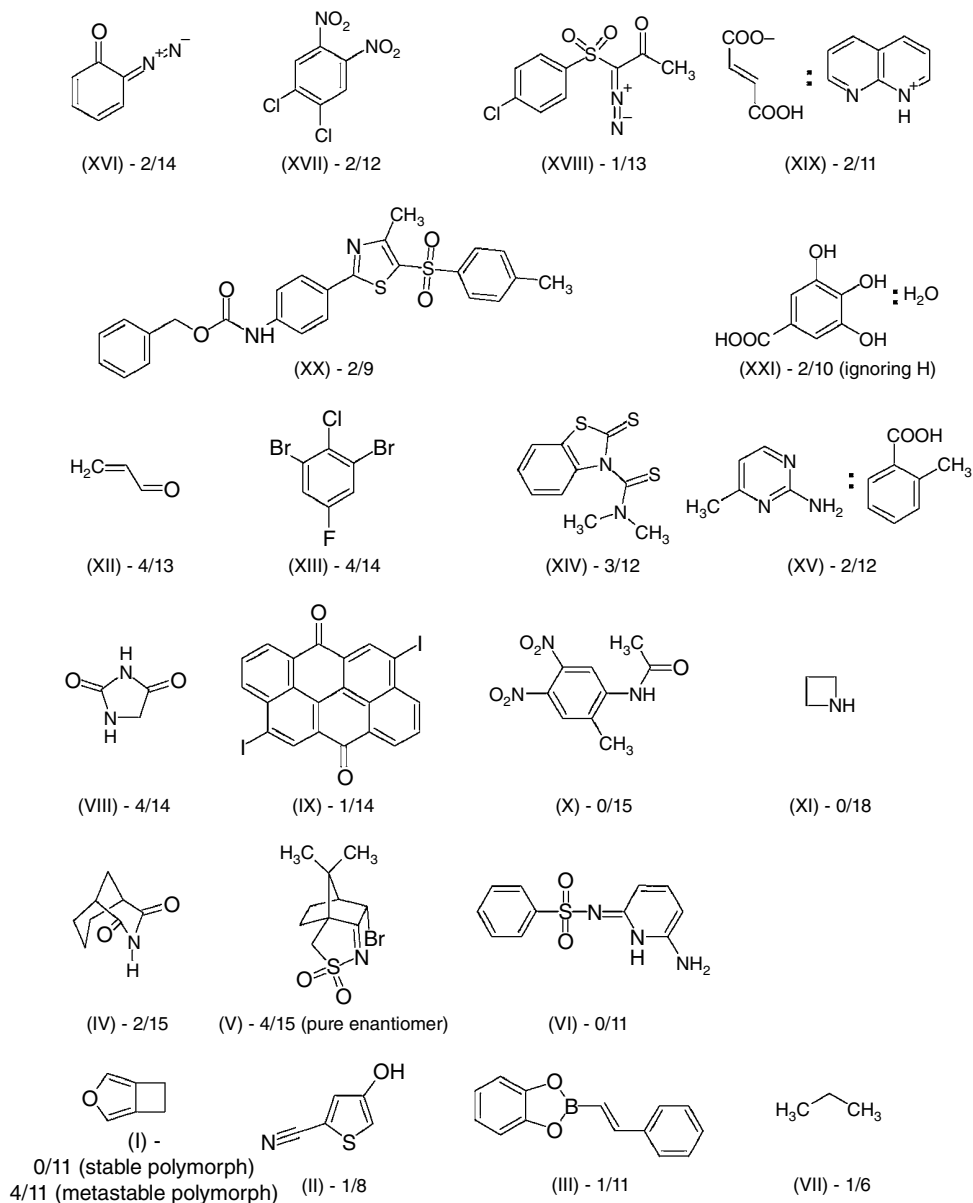


Figure 2.1 Molecules used in the CCDC blind tests of crystal structure prediction. The Roman numerals denoting the targets are approximately in year order: I–III and VII CSP1999 [15], IV–VI CSP2001 [16], VIII–XI CSP2004 [17], XII–XV CSP2007 [18], and XVI–XXI CSP2010 [19]. The success rate is given as x/y, where x of the y groups which submitted three predictions included the experimental structure. For XXI the challenge was to predict further polymorphs.

all four targets [20]. In the following test, the variety of target systems was increased to include a molecular salt, polymorphs of a hydrate and a molecule of a size that is more relevant to pharmaceutical development ($C_{25}H_{22}N_2O_4S_2$, XX in Figure 2.1). The crystal structure of this “model pharmaceutical” required a significant adaption of the methodology and was successfully predicted by two groups [21] but not by the approach which had been successful for the smaller molecules. Hence, the methodology of CSP studies is still actively evolving and is a challenge to computational chemistry methods. Future blind tests will help to evaluate progress, with computational costs (currently measured in CPU years for larger molecules) being only part of the challenge.

Polymorphism has always been acknowledged as a complicating factor in the interpretation of blind test results. Indeed further experimentation after blind tests found novel polymorphs for XXI [22], IV [23] and VI [24]. Whilst the thermodynamically most stable structure has to be found, which of the structures that are competitive in energy should correspond to polymorphs? CSP methods usually generate more plausible crystal structures than observed polymorphs, raising many questions about organic crystallisation [25]. This has led to the concept of a crystal energy landscape, a set of structures that are sufficiently low in energy to be potential polymorphs [26], and the question as to how these energy landscapes relate to the experimental crystal structures that the molecule could adopt. More practically, how can the calculated crystal energy landscapes help establish the true diversity of solid forms and act as a complement to other polymorph screening techniques?

Thus this chapter is divided into two sections. First, the general principles behind the computational approaches [27] that have been successful in blind tests will be outlined, with particular emphasis on the challenges for pharmaceutical molecules with their greater structural complexity. Pharmaceutical applications of CSP differ from those of computational materials design, where the aim is to suggest molecules whose crystals will have particular properties and avoid the synthesis of unpromising molecules. For example, an isolated molecule can have a large nonlinear optical coefficient, but if it crystallises in a centrosymmetric space group, the crystalline material will not be optically active. Molecular electronics, energetics, pigments and porous frameworks are other classes of functional materials where CSP methods have been applied. The blind tests are more closely aligned with the materials design problem, whereas for pharmaceutical applications, there may already be relevant experimental information that can be used to focus computational efforts, or known problems that need to be understood at the molecular level. The second section will therefore review some recent work where the crystal energy landscapes have been used as a complement to detailed experimental work on model pharmaceuticals, which indicates the potential use of CSP studies to complement experimental solid form screening.

2.2 CSP Methods for Generating Crystal Energy Landscapes

CSP methods [28] based on searching for the most thermodynamically stable crystal structures have to compromise between the number and range of crystal structures considered and the approximations used in evaluating the crystal energy. Current methods are based on the lattice energy as an approximation to the crystal energy, that is the energy of a completely ordered crystal at 0 K ignoring zero-point vibrational effects. This is only seeking the group of energetically favourable crystal structures and does not necessarily give the