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Introduction to Computational Pharmaceutics

Nannan Wang[1], Wei Wang[1], Hao Zhong[1], and Defang Ouyang[1,2]

[1]State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China
[2]Department of Public Health and Medicinal Administration, Faculty of Health Sciences (FHS), University of Macau, Macau, China

Acronyms

3D	three-dimensional
ADME	absorption, distribution, metabolism, and excretion
AI	artificial intelligence
ANDA	abbreviated new drug application
CFD	computational fluid dynamics
DDS	drug delivery systems
DEM	discrete element method
FDA	food and drug administration
ISPE	the international society for pharmaceutical engineering
MD	molecular dynamics

Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0, First Edition.
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MDI	pressurized metered dose inhaler
MIDD	model-informed drug development
NDA	new drug application
NME	new molecular entity
PBPK	physiologically based pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
QM	quantum mechanics
R&D	research and development

1.1 Current Pharmaceutical Research

Modern pharmaceutics, closely related to novel dosage forms and drug delivery systems (DDSs), has experienced a dramatic transformation over the past 70 years. In 1952, the development of the first 12-hour drug release formulation with Spansule® technology by Smith Kline & French initiated the history of modern pharmaceutics [1]. The progress of modern pharmaceutics made during the past 70 years could be divided into two generations [2, 3]. During the first generation (1950s–1980s), physical pharmacy, developed by combining the basic principles of physical chemistry with pharmacy, mainly focused on building the controlled-release preparations. During this period, drug delivery technologies were developed rapidly and achieved great success in clinical application, including oral sustained-release preparations, transdermal patch (Scop®) [4], and pressurized metered dose inhaler (MDI) [5]. The attention of the second generation (1980s–2010s) was dedicated to the development of advanced drug delivery systems. In the second generation of drug delivery technologies, several advanced approaches were widely investigated, including nanotechnology-based drug delivery systems, self-regulated drug delivery systems, and long-term depot formulations. However, due to biological barriers of the human body, the introduction of clinical formulations was significantly hindered and success rates were limited [6].

Nowadays, there is an obvious gap between the input of research and development (R&D) and the output of new molecular entities (NMEs). The costs of NMEs are growing significantly at an average rate of 13.4% per year [7]. However, the success rate of NMEs in clinical trials is merely about 10%. Research in 2007 involving 68 approved drugs reveals that it takes 15 years [8] and up to 2558 million dollars on average to bring a single NME to market [9]. As shown in Figure 1.1, only 37 NMEs were approved by the US Food and Drug Administration (FDA) in 2022 and the annual approval number remains at 20–50 compounds a year during the past 30 years despite the exponentially increasing resources invested, a phenomenon known as “Eroom’s law” [10]. Moreover, the current pharmaceutical products exhibit a far from optimal performance in clinical practice due to their low solubility, poor stability, and poor targeting effect. Theoretically, developing a novel formulation only costs a tiny fraction of the billions spent on each NME, and it only takes 3–4 years overall, which pushed many pharmaceutical companies to advanced drug delivery systems.

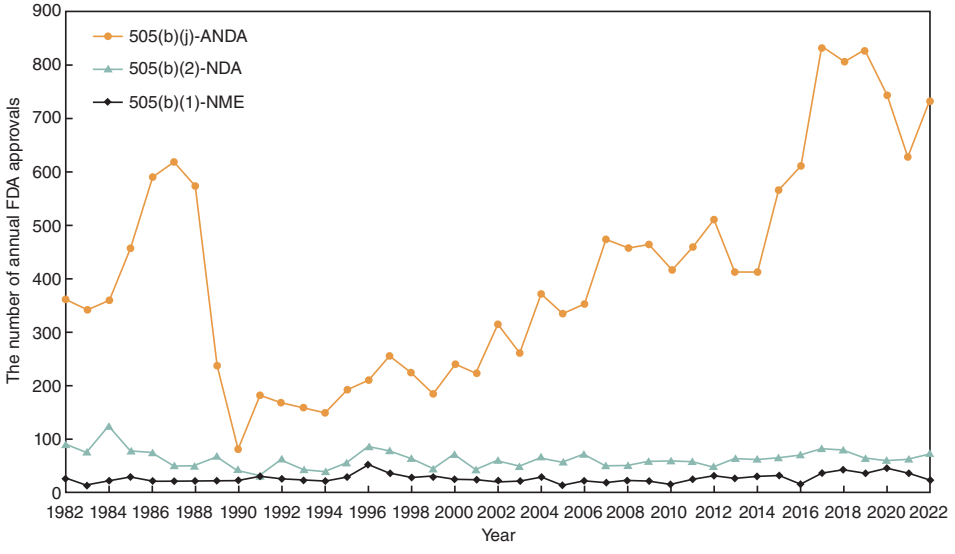

Figure 1.1 *The number of annual FDA approvals: (1) 505(b)(1)-NME: the approval of new molecular entities under section 505(b)(1); (2) 505(b)(2)-NDA: the approval of modified new drugs under section 505(b)(2), including new active ingredient, new dosage form, new combination, new formulation, or new indication; (3) 505(b)(j)-ANDA: the approval of abbreviated new drug applications under section 505(b)(j).*

Academic research in pharmaceutics has achieved remarkable progress in the past 40 years. As shown in Figure 1.2a, a total of 141,523 papers were published in pharmaceutical SCI journals with an impact factor above 1 between 1980 and 2022, showing a stable increase trend. The publication number in 2022 has reached up to 8420, almost 5.5 times higher than that in 1980 (1523). However, the clinical success rate (the ratio of marketed drug products to clinical trials) of advanced drug delivery systems was even lower than that of NMEs (10%) [11]. The main reason is that traditional R&D of pharmaceutical formulations still relies on the inefficient trial-and-error pattern, which lacks the focus and understanding of the multiscale interactions between the drug delivery system and the biological system.

The challenges of the high cost, long period, and low success rate bring about a question, that is, how to improve the efficiency of R&D of drug products. The current low efficiency of drug formulation development should be attributed to the conflict between the pharmaceutics principles and the traditional drug formulation development paradigm. Pharmaceutical research is essentially a multi-objective optimization task in the high-dimensional space consisting of material properties and process parameters. It has been estimated that the dimensionality of the space for formulation development can be as high as 10^{25}–10^{30} [12]. It is highly inefficient to perform trial-and-error tests in such a high-dimensional space. A straightforward idea is that knowing the basic principles in drug formulations in advance of production and testing should be cheaper than the endless trial-and-error tests relying on the favor of Lady Luck. Integrating the understanding of both products and processes into the design of drugs to improve their qualities is also encouraged in the philosophy of Quality by Design promoted by the US Food and Drug Administration.

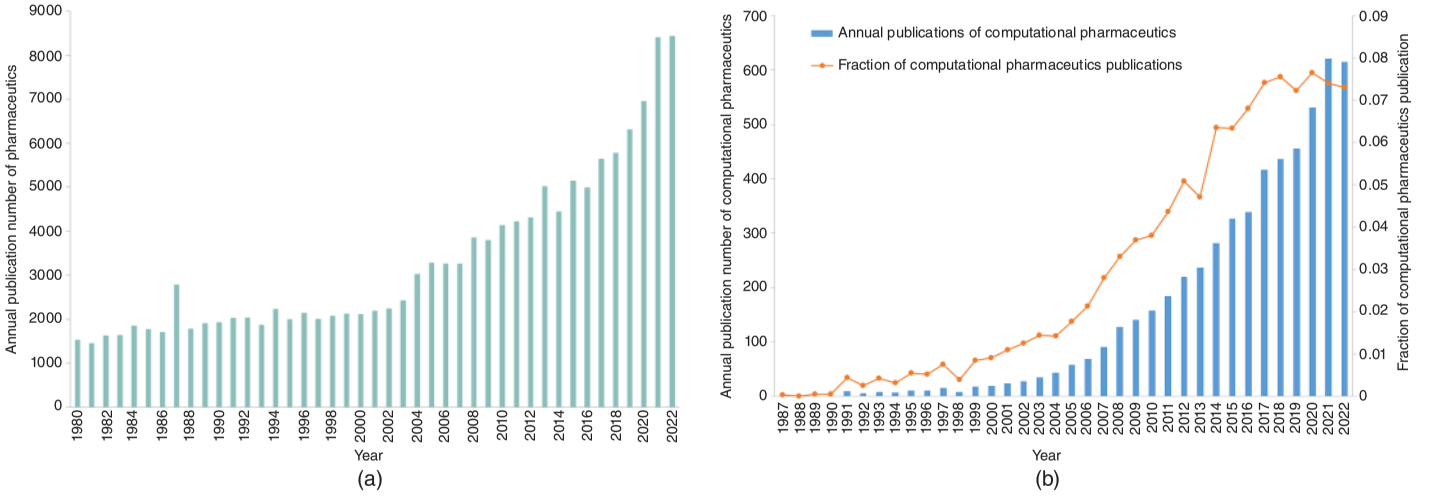

Figure 1.2 *(a) The annual publication number of pharmaceutics from 1980 to 2022. (b) The annual publication number of computational pharmaceutics and the fraction it represents out of all pharmaceutics publications. The number of publications of computational pharmaceutics in the year from 1987 to 1990 are 1, 0, 1, and 1, respectively.*

1.2 What is Computational Pharmaceutics?

Over the past decade, leaps in computing power are powering digital transformation in all sectors, and the pharmaceutical industry is no exception. The incorporation of artificial intelligence (AI) and multiscale modeling in drug formulation development has led to the emergence of a novel field known as "Computational Pharmaceutics" [12]. As shown in Figure 1.3, distinguished from conventional "screen-verify-re-screen" formulation development procedures, computational pharmaceutics emphasizes the computer-driven "understand-design-verify-optimize" formulation design paradigm [13]. By leveraging modeling and simulation tools to comprehensively comprehend the mechanisms of drug delivery, coupled with the potent design and optimization algorithms of AI, the concept of Quality by Design is being well implemented in computational pharmaceutics. This approach is expected to not only enhance the effectiveness of drug formulation development but also facilitate the objective-oriented and personalized drug development.

The commonly used tools in computational pharmaceutics include machine learning or AI, quantum mechanics (QM), molecular dynamics (MD) simulation, mathematical modeling, process simulation, and physiologically based pharmacokinetic (PBPK) modeling. By training models on existing data, machine learning or AI algorithms can uncover the underlying relationships and make predictions for new scenarios. QM uses the spatial electron density of molecules and functions of quantum chemistry to precisely calculate molecular properties and changes in chemical reactions. MD simulation is based on the potential energy within and between molecules and Newton's laws of motion to simulate and analyze the dynamic change in structures of the molecules and the constituted system. Mathematical modeling uses mathematical equations to describe macroscopic processes. Mathematical equations are the base of many types of simulations; however, the term "mathematical modeling" is usually accompanied by simulations of dissolution

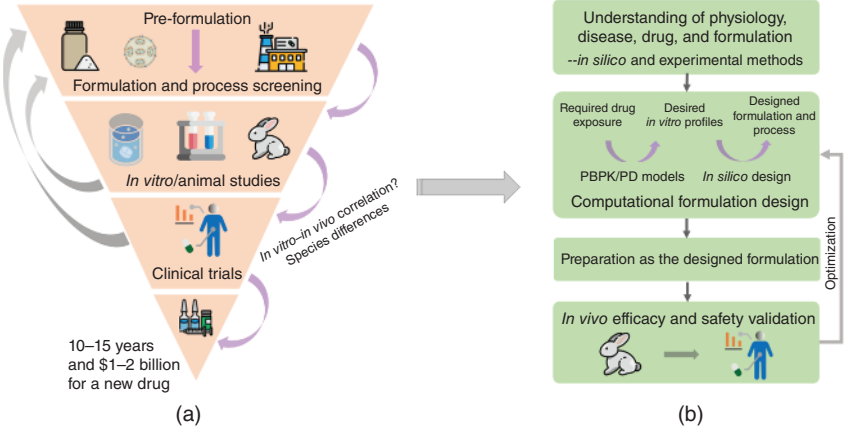

Figure 1.3 *Pharmaceutical formulation development paradigm shift prompted by computational pharmaceutics. (a) Conventional drug formulation development procedures: "screen-verify-re-screen" and (b) computer-driven drug formulation design framework: "understand-design-verify-optimize."*

and precipitation. Process simulation is to simulate the change in materials during the drug process in the manufacturing pipelines, and the involved techniques include computational fluid dynamics (CFD), discrete element method (DEM), and automatic monitoring systems trained from data with statistical algorithms. PBPK is a method of using a set of differential equations involving pharmaceutical and physiological parameters to simulate the pharmacokinetics of drug administration. Besides, if the pharmacokinetic/pharmacodynamic (PK/PD) relationship is known, PBPK/PD modeling is also possible.

Nowadays, research about computational pharmaceutics is increasingly getting popular. Using the same strategy as in the article [12] and searching the publications in the Web of Sciences up to the year 2022, 5547 papers were found. Among these publications, 85.2% (4724) of them are research articles, while review papers occupy 10.1% (590) and other types take around 5%. The number of publications per year is shown in Figure 1.2b. In the past decades, both the annual publication number for the field of computational pharmaceutics and its fraction in all pharmaceutics publications present rapid increases, especially from the year 2000. The number of publications in 2022 has exceeded 600.

These investigations present a landscape of the applications with computational pharmaceutics, as shown in Figure 1.4. The picture is that all stages of drug development can involve modeling technologies. AI or machine learning delves into the relationship underlying the data; thus, it can be used in nearly all situations only if the data is properly collected. QM and MD simulations are microscopic investigation techniques used to study the mechanisms of biomolecules, drug molecules, excipients, and their interactions. When faced with problems on a larger scale, QM and MD are not applicable because their calculation precision is too high, and the computation power of current machines does not support the simulation of too large systems. In such cases, methods based on mathematical modeling have to be used. The available mathematical equations cover processes like solid dissolution, molecule diffusion, flow of fluid or powder, particle collision, and ADME (absorption, distribution, metabolism, excretion) of drugs. These equations correspond to special problems in the stages of formulation development, product process, and clinics.

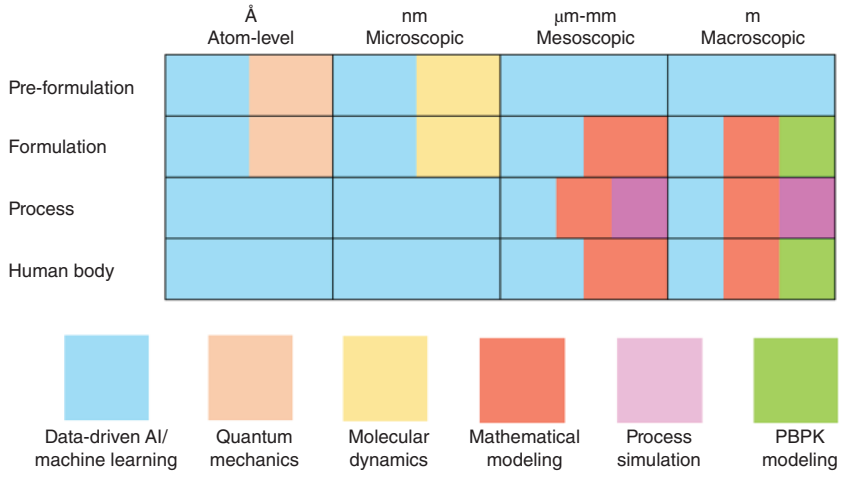

Figure 1.4 *Multi–level modeling techniques in computational pharmaceutics.*

1.3 About This Book

Inspired by the progress and prospects of computational pharmaceutics, we edited the first book titled *Computational Pharmaceutics: Application of Molecular Modeling in Drug Delivery* in 2015, published by the *Wiley* Press. The first edition of *Computational Pharmaceutics* mainly introduced the role of molecular modeling in the development of different pharmaceutical dosage forms. Recent advancements in computing power have opened new avenues for molecular modeling in pharmaceutics. Additionally, quantitative pharmacology research has spurred innovative ideas for clinical-oriented computational drug formulation development. Notably, the rapid growth of AI has infused computational pharmaceutics with renewed vigor. Moreover, computational pharmaceutics is not solely an academic concept, as a growing number of leading pharmaceutical companies and regulatory agencies have adopted it in the industrial sector in recent years [14, 15]. It offers a great driving force to shift the paradigm of drug development. In 2017, the International Society for Pharmaceutical Engineering (ISPE) proposed the *Pharma 4.0* initiative, aiming to integrate digital, intelligent, and automated technologies into the entire life cycle of drug development. The FDA also encourages the model-informed drug development [16] and prompt AI in drug development and manufacture. Computational pharmaceutics entered the fast lane of development in the *Pharma 4.0* era, and various research branches have accumulated many valuable research results. In response to the enthusiastic expectations of readers, the second edition, titled *Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0*, aims to introduce the cutting-edge progress of computational pharmaceutics in the past decade and provide the future perspective in the *Pharma 4.0* era.

In this chapter, we first performed a big data analysis of the research achievements in pharmaceutics and computational pharmaceutics and briefly introduced the connotation of computational pharmaceutics. A systematic introduction to computational pharmaceutics can also be obtained from two recent review articles [12, 13]. The remaining chapters are organized into the following parts.

Methodology: Chapters 2–8 detail the main computational techniques and resources applied in pharmaceutics, including AI, molecular modeling, process simulation, PK/PD modeling, and database resources in drug development. The computational research methods for the fundamental theories of physical pharmaceutics (e.g. 3D solid-state structure calculations of compounds, dissolution theory of pharmaceutical formulations) are also presented in this part. The methodology section will help the reader to develop the theoretical basis and mindset of computational pharmaceutics.

Industrial applications and nanomedicines: The potential and value of computational pharmaceutics in the *Pharma 4.0* industrial upgradation scheme is proving itself. In the following Chapters 9–16, we invite experts with both industrial and academic backgrounds to discuss the applications, challenges, and prospects of computational pharmaceutics in the pharmaceutical industry and nanomedicine research. The topics covered include the role of AI, multiscale modeling as well as digital twins in the design, manufacturing, and clinical application of tablets, inhalation formulations, 3D printed drugs, and traditional Chinese medicines. Moreover, since nanomedicines have been one of the hotspots of pharmaceutical researches, computational techniques used for structure and property investigation,

drug loading and release mechanism exploration, drug–biological system interaction understanding of nanomedicines will also be discussed, including inorganic nanoparticles and dendrimers.

Regulatory sciences: The maturation of computational pharmaceutics in the *Pharma 4.0* era cannot be achieved without the parallel development of regulatory science. Chapter 17 introduces patent analysis research, which can provide regulatory science with intelligence on technological innovation and market dynamics. Chapter 18 analyzes the positive attitude and regulatory requirements of global drug regulators toward model-informed drug development (MIDD) and AI in drug development.

Overall, this book was contributed by the leading experts in the field from the global academia, industry, and drug regulatory agencies, which provides a systematic introduction of the frontier technologies of computational pharmaceutics in the *Pharma 4.0* era and their applications in emerging pharmaceutical technologies. In addition, the regulatory science of computational pharmaceutics is also discussed.

The second edition of this book represents a significant departure from the first edition, as it provides a much more comprehensive introduction to computational techniques for pharmaceutical research, including AI, multiscale modeling, and quantitative pharmacology. The updated content covers a wider breadth and depth of material, and each chapter includes figures, formulas, cases, references, and other useful resources to cater to readers of all levels, from introductory to expert. This book is an invaluable resource for those seeking to develop their skills in computational pharmaceutics, and it is targeted toward pharmaceutical scientists, computational chemists, and computer scientists, while medicinal chemists, clinical pharmacists, material scientists, and nanotechnology specialists may also find it beneficial. Overall, we hope that this book will provide interested readers with a deeper understanding of computational pharmaceutics and inspire them to pursue new knowledge and ideas in this exciting field.

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