ADVANCES IN PHARMACEUTICAL TECHNOLOGY

Editor
Defang Ouyang

Exploring Computational Pharmaceutics - AI and Modeling in Pharma 4.0

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Preface

It is with great pleasure that we present the second edition of our book, *Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0*. This book builds upon the foundation laid by our previous work, *Computational Pharmaceutics: Application of Molecular Modeling in Drug Delivery*, published by the Wiley Press in 2015.

The pharmaceutical industry is in a constant state of evolution, presenting new daily challenges and opportunities. With the advent of Pharma 4.0 and the increasing importance of artificial intelligence and modeling in drug discovery and development, we felt it was necessary to update our previous work to reflect these changes.

In this book, we explore the latest advancements in computational pharmaceutics, including the use of AI and machine learning in drug formulation, the application of multi-scale modeling in drug delivery, and the integration of these technologies into the drug development process. We hope that this book will serve as a valuable resource for scientists, students, and professionals in the field of pharmaceutics.

We would like to express our gratitude to our collaborators who have contributed to this book, as well as to the Wiley Press for their continued support. We hope that this book will inspire further research and innovation in the field of computational pharmaceutics, and we look forward to seeing the impact that these technologies will have on the future of drug discovery and development.

29 March 2024

Defang Ouyang
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1

Introduction to Computational Pharmaceutics

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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

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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.

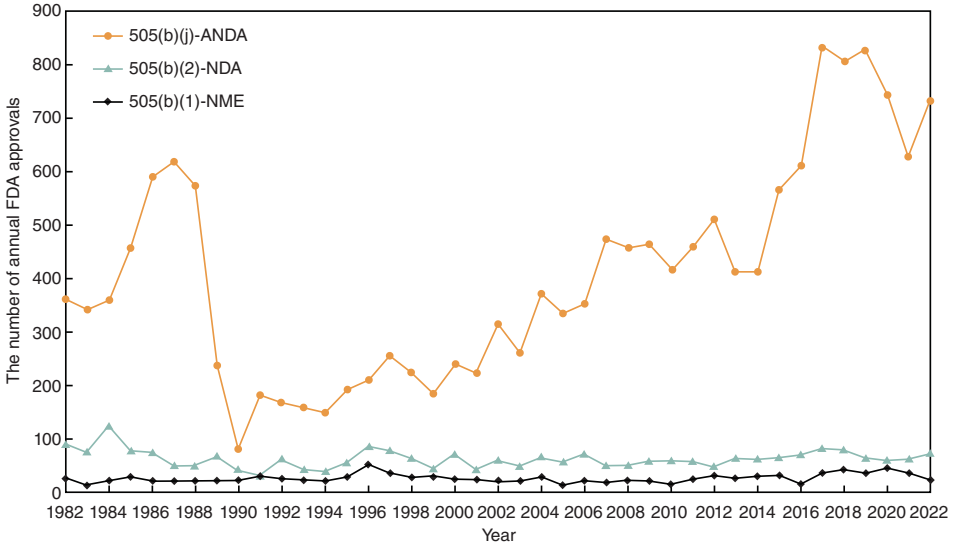

Figure 1.1 *The number of annual FDA approvals: (1) 505(b)(1)-NME: the approval of new molecular entities under section 505(b)(1); (2) 505(b)(2)-NDA: the approval of modified new drugs under section 505(b)(2), including new active ingredient, new dosage form, new combination, new formulation, or new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

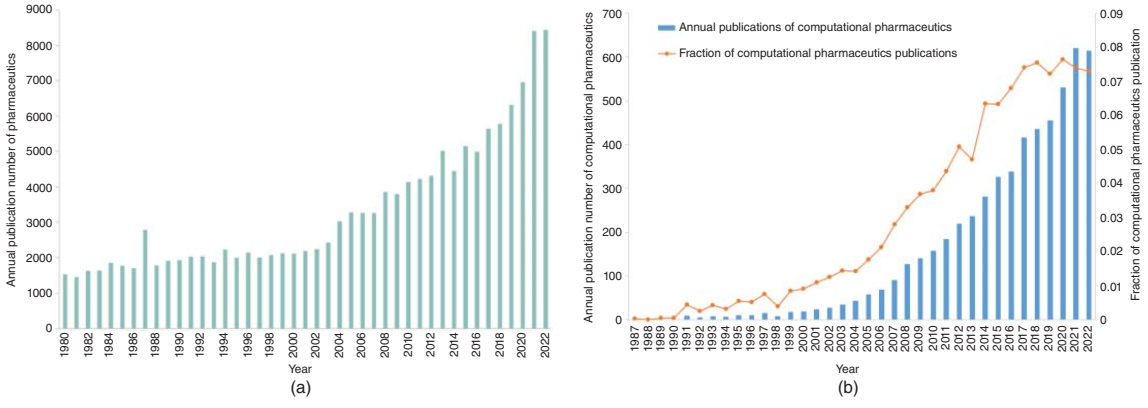

Figure 1.2 *(a) The annual publication number of pharmaceutics from 1980 to 2022. (b) The annual publication number of computational pharmaceutics and the fraction it represents out of all pharmaceutics publications. The number of publications of computational pharmaceutics in the year from 1987 to 1990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

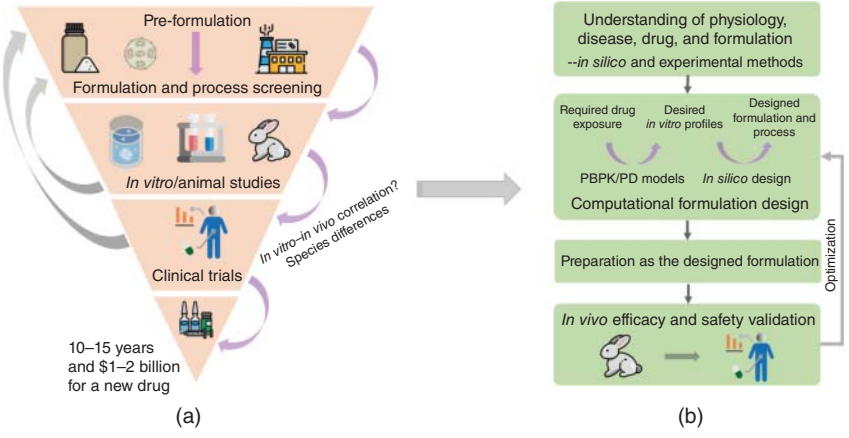

Figure 1.3 *Pharmaceutical formulation development paradigm shift prompted by computational pharmaceutics. (a) Conventional drug formulation development procedures: "screen-verify-re-screen" and (b) computer-driven drug formulation design framework: "understand-design-verify-optimize."*

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.

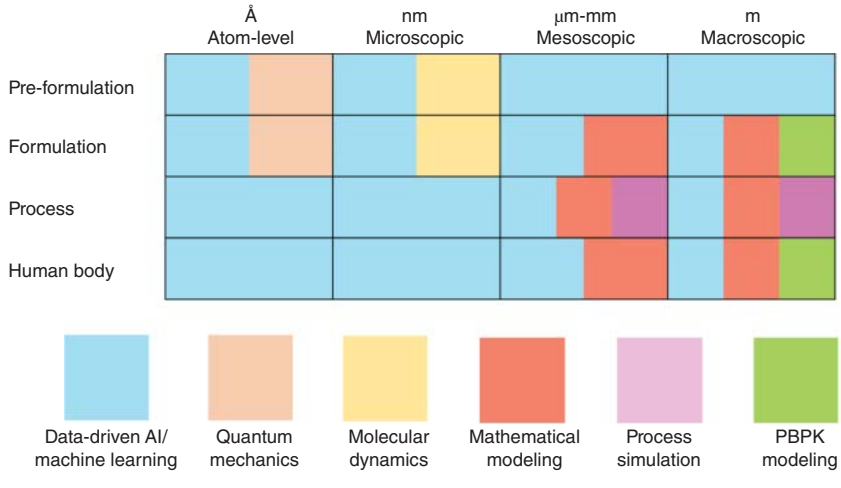

Figure 1.4 *Multi–level modeling techniques in computational pharmaceutics.*