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Review article

# Computational pharmaceutics - A new paradigm of drug delivery

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ABSTRACT

In recent decades pharmaceutics and drug delivery have become increasingly critical in the pharmaceutical industry due to longer time, higher cost, and less productivity of new molecular entities (NMEs). However, current formulation development still relies on traditional trial-and-error experiments, which are time-consuming, costly, and unpredictable. With the exponential growth of computing capability and algorithms, in recent ten years, a new discipline named "computational pharmaceutics" integrates with big data, artificial intelligence, and multi-scale modeling techniques into pharmaceutics, which offered great potential to shift the paradigm of drug delivery. Computational pharmaceutics can provide multi-scale lenses to pharmaceutical scientists, revealing physical, chemical, mathematical, and data-driven details ranging across pre-formulation studies, formulation screening, in vivo prediction in the human body, and precision medicine in the clinic. The present paper provides a comprehensive and detailed review in all areas of computational pharmaceutics and "Pharma 4.0", including artificial intelligence and machine learning algorithms, molecular modeling, mathematical modeling, process simulation, and physiologically based pharmacokinetic (PBPK) modeling. We not only summarized the theories and progress of these technologies but also discussed the regulatory requirements, current challenges, and future perspectives in the area, such as talent training and a culture change in the future pharmaceutical industry.

## 1. Current pharmaceutics

It is widely recognized that active drug molecules should be made to proper formulations or drug delivery systems or dosage forms in the clinic. In recent years, the research and development (R&D) efficiency of New Molecular Entities (NMEs), estimated in terms of the number of NMEs brought to market by the pharmaceutical industries per billion US dollars of R&D spending, has dropped gradually [1]. Research in 2007 about 68 approved drugs reveals that it takes 15 years [2] and up to 2558 million [3] dollars on average to bring a single NME to market. The annual number of NMEs approved by the US Food and Drug Administration (FDA) struggles continuously at 20–50 compounds. In addition, the majority of current approved NMEs are far from the optimal clinic performance, limited by low solubility, poor stability, and poor targeting effect. Approximately 40% of NMEs are suffering from low water-soluble and bioavailability related challenges [4]. As the productivity of NMEs continues to stagnate, novel dosage forms are entering the mainstream in the pharmaceutical industry. The R&D of novel formulations is significantly more time- and cost-effective than the R&D of NMEs. At the same time, utilizing drug delivery systems (DDS) can ameliorate the pharmacological characteristics of NMEs, such as pharmacokinetics (PK) and pharmacodynamics (PD).

Modern pharmaceutics, closely associated with pharmaceutical dosage forms and drug delivery systems, has been experienced over 60-year development since the 1950s. In 1952, SmithKline successfully introduced the first 12-h controlled release formulation with Spansule® technology [5], which represented the beginning of modern pharmaceutics. Generally speaking, modern pharmaceutics could be classified into two generations [6,7]. During the first generation (the 1950s–1980s), the basic principles of physical chemistry were integrated with pharmacy into a new research area, "physical pharmacy". Prof. Takeru Higuchi was a widely recognized pioneer in the area [8]. During the period, many new dosage forms, including the pressurized metered dose inhaler (MDI) [9] and transdermal patch product (Scop®) [10], were successfully developed and achieved great success from basic research to clinical applications.

The second-generation (1980's-2010's) technologies fall into the category of advanced drug delivery systems. With the development of

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recombinant DNA technology, human insulin was approved by FDA in 1982. After that, numerous biopharmaceutical products entered the clinic. Therefore, new formulations of biomacromolecules were developed to deliver peptides and proteins for months, such as biodegradable poly(lactic-co-glycolic acid)(PLGA) microsphere Decapeptyl® (1986), solid implant Zoladex® Depot (1989), and Polyethylene glycol(PEG)-ylated protein Adagen®(1990) [11]. During the period, nanotechnology-based DDS also became the research hotspot, and thousands of papers were published annually. However, except for the traditional liposome and nanocrystal formulations [12,13], the so-called nanomedicines were very limited to transform into clinic products, which caused wide controversy [14]. The possible reason is that current nanomedicine cannot effectively reach the target site due to the complexity of the human body [15]. In the recent decade, drug delivery research started to take advantage of the computer to develop smart and targeted delivery, such as 3D-print technology and digital drugs.

Although pharmaceutics has made significant progress in the decades, the R&D of formulation still relies on traditional trial-and-error experiments, which are time-consuming, costly, and unpredictable. The conventional formulation design needs to experience pre-formulation, formulation screening, and process scale-up and in-vivo study. If the result is unsatisfactory, the whole process needs to be re-tested.

In fact, the plight of pharmaceutics nowadays is like what the whole bioscience faces. The UK Research and Innovation-Biotechnology and Biological Sciences Research Council (UKRI-BBSRC) states in the review [16] that bioscience has to handle the data sharply being larger in scale and more complicated. With the exponential development of computing capability and algorithms, current computer modeling and algorithm can simulate or analyze complex systems. Thus, a data-intensive research pattern, which applies computational analysis and modeling methods to make data "Findable Accessible Interoperable and Re-usable", is deemed a promising strategy to process the expanding "data-rich" bioscience. As for pharmaceutics, since it is a multidisciplinary science and decades of its development have produced a tremendous amount of data, the data-intensive approach should also facilitate the R&D of formulations.

## 2. What is computational pharmaceutics?

In the last decade, a new discipline named "***computational pharmaceutics***" integrates artificial intelligence and multi-scale modeling techniques into pharmaceutics, offering great potential to shift the paradigm of current formulation development [17]. Computational pharmaceutics is able to provide multi-scale lenses to pharmaceutical scientists, revealing physical, chemical, mathematical, and data-driven details ranging across chemical stability, polymorphism, formulation screening, and precision medicine. Computational approaches play an essential role in all areas of pharmaceutics, involving but not limited to quantum mechanics (QM), molecular dynamics simulation, mathematical modeling, physiologically based pharmacokinetic (PBPK) modeling, process simulation, artificial intelligence (AI), and machine learning algorithms, as shown in Fig. 1.

QM provides an accurate description of electrons' spatial positions, other atomic- and molecular-scale objects by the Schrödinger equation. It can predict the structural and physicochemical properties of molecules. Molecular dynamics (MD) simulation mimics atoms and molecules' physical motion under Newton's physics laws. Molecular modeling is able to investigate the structural, dynamic, and energetic aspects of drug/excipient and the molecular mechanism of formulations based on molecular mechanics and the empirical force field. Process modeling is the numerical simulation of a physical process in such as the manufacturing line. PBPK simulation can predict the pharmacokinetic/pharmacodynamic (PK/PD) behavior of formulation in humans. AI and machine learning algorithms are able to make data-driven predictions by an algorithm from large amounts of cumulated experimental data to build the quantitative formulation prediction model. A well-designed AI system can significantly speed up the development, optimize formulations, save the cost, keep products consistent, and accumulate and preserve the specific knowledge and expertise from formulation experts [18].

These computational methods are increasingly associated with pharmaceutical research in the recent three decades. Searching with the strategy [TOPIC: ("mathematical model*" OR "computer model*" OR "computer simulation" OR "process simulation" OR "molecular model*"

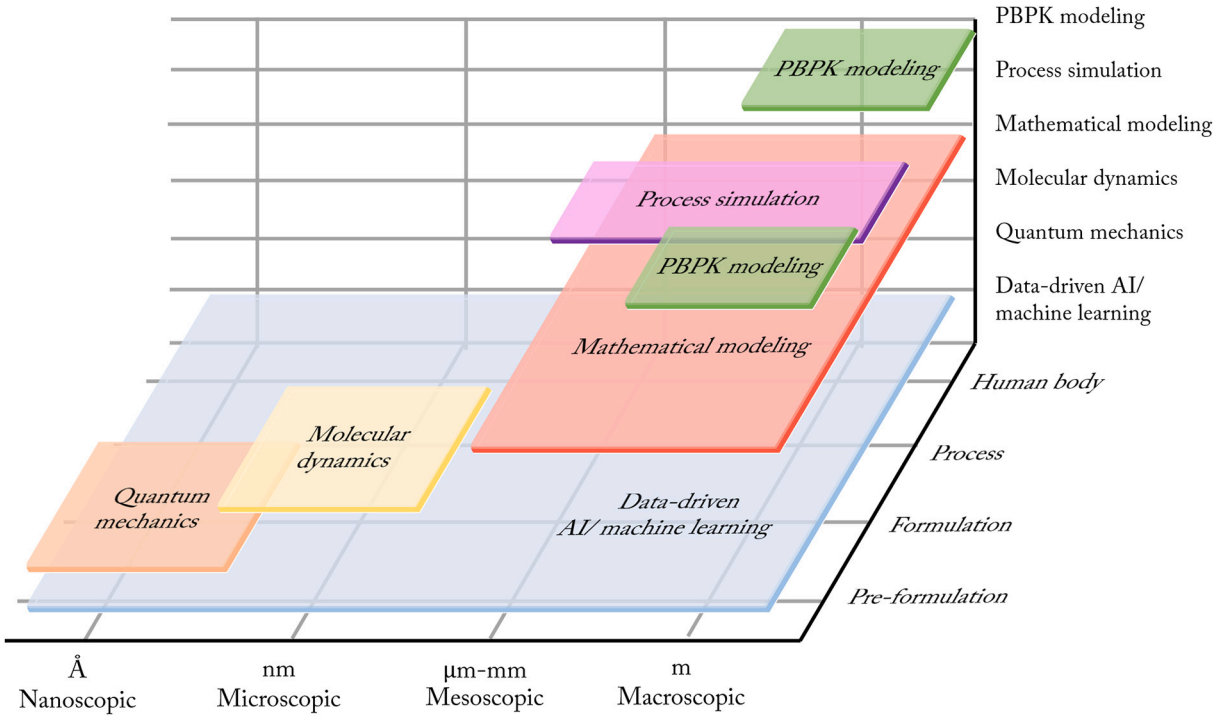


**Fig. 1.** Multi-scale modeling and AI in computational pharmaceutics.

OR "molecular dynamics" OR "molecular simulation" OR "artificial intelligence" OR "machine learning" OR "PBPK model*" OR "physiologically-based pharmacokinetic model*") AND TOPIC: ("drug delivery" OR "drug formulation" OR pharmaceutics)] in the Web of Sciences, 4277 publications up to 2020 have been obtained, as shown in Fig. 2.

Among 4277 publications, 85% of publications are research articles, while review papers occupy 9% and other types take 6%. Fig. 2 showed the annual publication number in the computational pharmaceutics area increases steadily since 2000 and rise sharply in recent ten years, reaching over 500 papers in 2020. Table 1 lists the top 10 countries or regions in the area. The USA ranks first, and China follows second. There are several special issues about computational pharmaceutics area, including "Computational drug delivery" (2006), "Modeling the human skin barrier—Towards a better understanding of dermal absorption" (2013), "Mathematical modeling of systems pharmacogenomics towards personalized drug delivery" (2013) in <Advanced Drug Delivery Review>, "Mathematical modeling in drug delivery system" (2011) in <International Journal of Pharmaceutics>, "Fifty-Eight Years and Counting: High-Impact Publishing in Computational Pharmaceutical Sciences"(2019) in <Journal of Pharmaceutical Sciences>.

Consistent with this trend, several big research funding/grants about computational pharmaceutics in the world were launched. Advanced Digital Design of Pharmaceutical Therapeutics (ADDoPT) is a four-year £20.4 m project aiming to transform the UK pharmaceutical industry by enabling the future digital design of innovative medicine manufacturing processes. The project Oral biopharmaceutics tools (OrBiTo), started in 2012 and involved 29 partners from academic and industrial fields as the consortium, aims to "deliver a framework for the rational application of predictive biopharmaceutics tools for oral drug delivery". This project highlights PBPK and MD modeling as predictive tools and suggests applying AI technology to utilize datasets efficiently in the future.

The regulatory agencies, such as the FDA, consider applications of computational methods to pharmaceutics should promote the product quality, since this approach highlights the process understanding in product design, conforming to the quality by design (QbD) strategy [19]. The FDA recently announced the Knowledge-aided Assessment & Structured Application (KASA) system [20], where rules and algorithms based on the data of the product, manufacturing, and facilities will be used to assess drug products. Besides, the newly put forward approaches, model-informed drug development (MIDD) [21] or model-informed drug discovery and development (MID3) [22], show the positive attitude of the FDA, the European Medicines Agency (EMA). A similar report was also published by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) [23] in 2017. In China, the Center for Drug Evaluation (CDE) has been collecting suggestions for guidance for MIDD. These documents mainly highlight the application of PK modeling in drug development.

**Table 1**
Top 10 countries or regions within computational pharmaceutics area.

| Country | Publications number |
|---|---|
| USA | 1318 |
| China | 593 |
| India | 346 |
| England | 301 |
| Iran | 286 |
| Italy | 245 |
| Germany | 221 |
| France | 199 |
| Australia | 134 |
| Canada | 129 |

As computational methods are changing the way of the drug R&D paradigm and the way we are thinking, there is a need to review the existing applications of various in silico tools in the pharmaceutical field to clue where we are and how we go further. This present review primarily aims to summarize pharmaceutical investigations involving AI technology, molecular modeling, mathematical modeling, process simulation, and PBPK modeling. Each method has its advantages and disadvantages so that the better way is to integrate various tools to solve problems in the future.

## 3. AI and machine learning

### 3.1. Introduction

The QbD strategy defined the design space as "the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality" [24]. It was well recognized that pharmaceutical product development is a high-dimensional optimization problem. It is estimated that the size of the

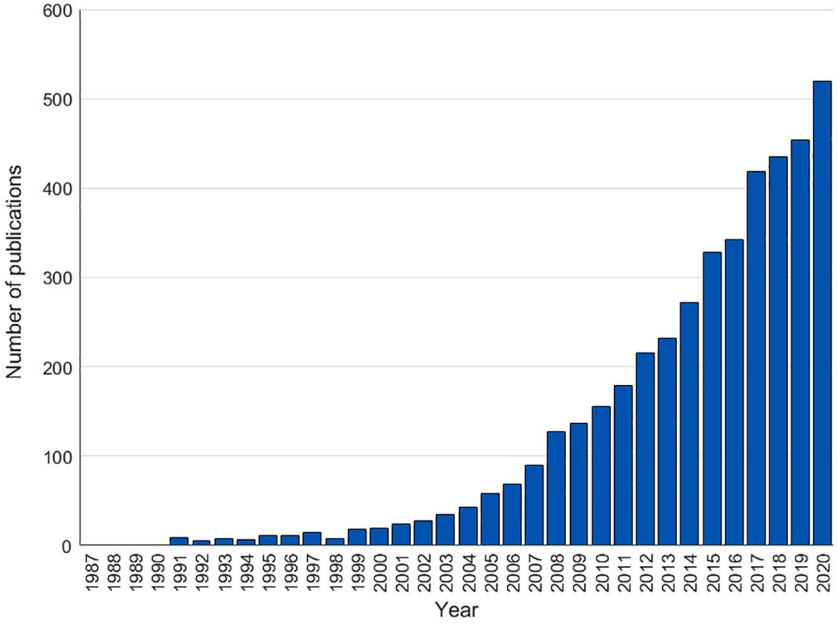


**Fig. 2.** Annual publication number in computational pharmaceutics area. The number of publication in1987, 19,881 1989, 1990 is 1, 0, 1, 1, respectively.

formulation space was around $10^{25}$–$10^{30}$ (please refer to the Supplementary Information for calculation details). In such a high-dimensional space, it was hard to predict and optimize the formulation only by scientists' limited experience. Therefore, there is plenty of improvement room to rationally design by leveraging the powerful fitting and generalization ability of statistical learning methods. It means significant time savings and resources reduction.

Machine learning is an important research branch of artificial intelligence (AI), which can fit high-dimensional non-linear correlation based on big data and find the influence of minor variance of inputs on the difference of targeted labels. AI has attracted a lot of people's attentions and is increasingly becoming the core engine and driver of a new round of industrial change, constantly generating new technologies. Currently, AI has been applied to many fields, such as finance, retail, and medicine [25].

AI is reported to be used in drug R&D at stages such as the development of active pharmaceutical ingredients (API), toxicology study, and clinical study, etc. Twenty-one leading pharmaceutical companies each have at least one application involving AI [26]. This trend even has attracted tech giants like Google, Microsoft into medicine [27]. Recently, the protein structure prediction tool AlphaFold2 from DeepMind shocks the world with its experiment-level precision [28], showing the potential of AI combined with biological science and pharmacy.

The utilization of AI in this area has attracted attention from experts in pharmaceutics. In fact, AI is not a new thing in pharmaceutical investigations. For example, in 1991, a study, which applied ANN to pharmaceutical formulation development, was published by Ajaz S. Hussain and co-workers [29]. An ANN model was trained to predict the drug release parameter, the dissolution half–time. Compared with the traditional response surface methodology, it was shown that ANN had higher accuracy, probably due to the higher data fitting ability of ANN. Recently, with more cutting-edge algorithms occurring, such as deep neural networks (DNN), ensemble learning, transfer learning, and so on, AI has promoted the R&D of numerous dosage forms, including but not limited to hydrophilic sustained-release matrix tablets, oral fast disintegrating film and tablets, cyclodextrin (CD) complex, amorphous solid dispersion (ASD), nanocrystals, and so on [18,30–38].

### 3.2. Expert system in pharmaceutics

The expert system was a research branch of AI. It was generally thought that an expert system is a kind of intelligent program that simulated human experts to solve specific kinds of domain problems. A well-designed and validated pharmaceutical expert system analyzed the properties of API and recommended the optimal formulations.

Currently, expert systems have been applied to various dosage forms, including solid dispersions, sustained-release, controlled-release dosage forms, micro pellet systems, and so on [39–41]. Osmotic pump tablets (OPT) delivered drugs at a constant rate for a long time, therefore reduced the dosing frequency and maintained a steady blood concentration. In 2011, the first expert system for a controlled release dosage form of bilayer push-pull osmotic pump tablets was proposed [39]. The neural network algorithm was used to predict drug release from OPT. The optimization strategy summarized from human experts' experience and logits was written as the nucleus of the inferencing engineer. An expert system utilizing the neural network and optimization strategy searched the optimal formulation of OPT step by step. In 2012, a special expert system using the SeDeM-ODT algorithm was proposed for the rational design of oral disintegrating tablets (ODT) [42]. It first used the SeDeM-ODT algorithm to preprocess the data of API physicochemical properties and process parameters to non-dimensional data. Then it utilized the processed data to predict drug release and subsequently searched the optimal formulation of ODT step by step. This expert system simultaneously optimized two properties, including direct compression and disintegrating ability. In addition, expert systems have been applied to pharmaceutical drug-excipient compatibility research at the pre-formulation stage. In 2021, the first expert system for pharmaceutical drug-excipient compatibility was developed [43]. A database and a knowledge base were constructed. The database including 532 drug-excipient incompatibility cases was extracted from literature. The drug-excipient compatibility knowledge and experts' experience were summarized as 60 rules in the knowledge base. Based on the database and knowledge base, the expert system provided four functions: basic data search, structural similarity-based data search, risk evaluation of drug substructures, and risk evaluation of drug-excipient incompatibility.

### 3.3. Machine learning in formulation development

Currently, some efforts have been made to apply AI techniques to pharmaceutical product development, including pre-formulation physicochemical property and activity prediction, *in vitro* drug release, physical stability, *in vivo* pharmacokinetic (PK) parameters, drug distribution, *in vivo-in vitro* correlation (IVIVC) and so on. Machine learning attracted attention because of its powerful fitting and prediction ability. Machine learning algorithms were used to predict the performance of various dosage forms, including ASD, CDs, nanoparticles, self-emulsifying DDS (SEDDS), and so on. Supplementary Table 1 summarized the progress. In addition, many machine learning techniques have been used to predict formulations or generate data, such as transfer learning, multitask learning, federated learning, generative adversarial networks, and interpretable machine learning methods.

ASD dispersed the APIs uniformly in the carrier in amorphous, microcrystalline, or other highly dispersed states. Amorphous improved the solubility, dissolution rate, and bioavailability of poorly soluble drugs. Solid dispersion has two main problems, physical stability and dissolution behaviors. In 2019, Run Han and co-workers applied machine learning methods to the prediction of the 3-month and 6 month physical stability of solid dispersion [44]. Eight learning algorithms were introduced to create models. 82.5% accuracy of the random forest model was further validated by experiments. Also, in 2021, in Hanlu Gao and co-workers' work, the dissolution behaviors of solid dispersion were investigated by machine learning [45]. The random forest algorithm was used to construct a classification model to distinguish two types of dissolution profiles of “spring-and-parachute” and “maintain supersaturation” with 85% accuracy, 86% sensitivity, and 85% specificity in 5-fold cross-validation. The random forest algorithm was used to construct a regression model to predict the time-dependent accumulative drug release with a mean absolute error of 7.78 in a 5-fold cross-validation.

CD complexation enhanced the solubility of insoluble drugs and improved bioavailability and stability. CDs and guest drug molecules formed CD complexation by the reversible binding. The binding free energy was a good indicator to estimate the binding strength. In 2019, the largest CD complexation binding free energy dataset covering 3000 formulations were collected by Qianqian Zhao and co-workers [46]. Eight types of CDs were included, and three machine learning algorithms were applied and compared. The results showed that the lightGBM model demonstrated the best performance of 1.38kI/mol mean absolute error. The feature importance obtained from lightGBM gained valuable insights that the minimum projection radius of APIs has a primary effect on the reversible binding.

Nanoparticles were found to have advantages in delivering drugs to the target cells or tissues. Various characteristics of nanoparticles account for the delivery, including the size, shape, chemical compositions, and surface chemistry of nanoparticles. However, designing the optimal nanoparticle DDS is challenging. There is an increasing number of experimental tests to probe the characteristics of nanoparticles in vitro, in vivo, and at the disease sites. In 2020, Yuan He and co-workers utilized machine learning techniques to predict nanocrystals [47]. 910 particle size data and 310 PDI data covered ball wet milling, high-pressure homogenization, and antisolvent precipitation methods.

LightGBM models demonstrated good performance for the nanocrystals produced by ball wet milling and high-pressure homogenization methods.

The SEDDS were composed of oil, surfactant, cosurfactant, and APIs. The selection of suitable emulsifying agents and stabilizers was a crucial step in the formulation development. In 2021, Haoshi Gao and co-workers collected a SEDDS dataset with 4495 formulation composition ratios [48]. Seven machine learning algorithms were used to construct models to distinguish whether the oil, surfactant, and cosurfactant could form the SEDDS. Compared to other machine learning algorithms, random forest showed the best accuracies of 91.3% accuracy, 92.0% sensitivity, and 90.7% specificity in a 5-fold cross-validation. A DOE method of central composite design (CCD) was used to further screen the ratios.

In pharmaceutics, small data is a common problem in the machine learning modeling process. Transfer learning utilized the big data in the source domain and transferred the learned knowledge to the target domain with limited data to enhance the performance. Multitask learning predicted the multiple tasks simultaneously and used the data of multiple tasks to learn the common network weights and knowledge. In 2019, an integrated transfer learning and multitask learning approach was developed to construct quantitative structure-activity relationship (QSAR) models for the prediction of the four human PK parameters by Zhuyifan Ye and co-workers [49]. Totally, the human PK data of 1104 listed small molecule drugs were collected, including oral bioavailability, plasma protein binding rate, apparent volume of distribution at steady-state, and elimination half-life. A pre-trained deep learning model was trained on bioactivity data with more than 30 million entries. The integrated transfer learning and multitask learning approach was used to fine-tune the model on the PK dataset. The results showed that the integrated approach enhanced the model generalizability.

Model interpretability was increasingly considered as important as model performance in formulation development. Though some post-hoc interpretable methods have been proposed, methods based on post-hoc analysis faced the concern of faithfulness. In 2021, attention-based DNNs were proposed for pharmaceutical formulation development by Zhuyifan Ye and co-workers [50]. Attention-based DNNs distinguished inputs, leading to higher accuracies than plain DNNs and generated interpretable attention weights for DNNs. Compared with post-hoc interpretable methods, the proposed approach had the advantages of providing global and local (sample-level and feature-level) interpretations, self-interpretable models, and having high faithfulness.

Besides *in silico* predicting pharmaceutical formulation performance, it was recognized that generating data using machine learning was of great significance, especially given some implicit parameters. Generative models estimated the joint probability distribution of data. For example, the description of nanoparticle distribution in targeted organisms was crucial for the R&D of nanomedicine. In 2021, Yuxia Tang and co-workers used deep generative networks to describe the nanoparticle distribution within T1 breast cancer tumors [51]. The conditional generative adversarial networks (cGAN) and pix-to-pix techniques were used to conditionally model the nanoparticle distributions. The generative network was trained on 27,775 breast cancer slide images.

### 3.4. AI in precision medicine

Since precision medicine was announced in 2015, this new term was getting a lot of attention. Trace to its source, precision medicine is derived from personalized medicine. Personalized medicine has a long history, which had reflected the individualization of medical treatment since ancient times. From personalized medicine to precision medicine, it has many impacts on disease prevention, diagnosis, and treatment. As announced by the National Institute of Health (NIH), in precision medicine, the importance of factors of individual genes, environment and lifestyle is increasing [52]. The role of AI in precision medicine is indispensable to predict which treatment is the best for a patient. Here we focused on the impact of AI in precision medicine and drug delivery, taking the right dose of insulin delivery for diabetes as an example. Patients with type 1 diabetes could be treated with insulin. The insulin pump is a type of automatic drug delivery equipment [53]. This automatic insulin delivery equipment has four components: AI control algorithm, continuous glucose monitoring sensor, drug delivery pump, and insulin. By closely monitoring the data of patients' meal time, types of food, and blood glucose, it delivers insulin at the right doses. It helps patients better control their blood glucose. This kind of healthcare achieved close monitoring, tailoring medical interventions, and dynamic modulation.

### 3.5. Current problems of AI in pharmaceutics

The recent development of AI techniques has played an essential role in the rational design and development of pharmaceutical products. The successful application of many AI technologies has shortened the development time, ensured the quality of products, and promoted the successful R&D of pharmaceutical products. However, during applied machine learning algorithms, a common problem was lacking data. The high cost of pharmaceutical experiments and lengthy research and optimization time caused this issue. Because big pharma companies usually strictly kept their data, the existing pharmaceutical data became isolated islands. In addition, people were no longer satisfied with only the good performance of machine learning models but hoped to understand the running mechanism behind the models. The interpretable machine learning methods could bring more deep insights for pharmaceutical formulation development. In the future, the further integration of the pharmaceutical industry and AI technologies will bring more opportunities for pharmaceutical research and development.

## 4. Molecular modeling

According to the timescale and length scale, molecular modeling mainly contains three different parts: quantum mechanics (QM), all-atom molecular dynamics (MD) simulation, and coarse-grained (CG) modeling, as shown in Fig. 3. Their applications to pharmaceutical studies are listed in Supplementary Table 2.

### 4.1. QM and its applications in pharmaceutics

Here, the QM refers primarily to quantum mechanical simulations and calculations using computer technology. Almost all properties of a molecule can be calculated by QM, such as structure, conformation, dipole moment, ionization potential, electron affinity, electron density, transition states, and reaction pathways. Besides, they can provide fundamental data on interatomic interactions in molecular dynamics, such as bond length, bond angle, interatomic interactions, and energy. Hence, QM is applicable to study relatively small systems, including molecule-to-molecule interactions and reactions involving bond breakage and formation [54].

In the development of PLGA contained drug delivery system, the QM method has been used to analyze the energy transition during the process of salted-out and PLGA crosslinking, which involves the interaction between PLGA and *N*,*N*-dimethyl formamide (DMF) solvent, water, and hydrochloric acid (HCl) [55]. The simulation result for 26 formulations produces profiles of matrix resilience, energy absorbed, and mass deflection, which is consistent with the experimental value. These results are important to judge the formulation stability when immersed in the phosphate-buffered saline solution.

QM also shows the application in lead optimization. It has been successfully adopted to select out the drug molecule with the highest solubility from a series of similar compounds [56]. The solubility of a molecule is correlated to the sum of the free energy change of crystal sublimation process and molecule hydration process, reflecting the molecule first overcome the lattice energy and then dissolves in water.

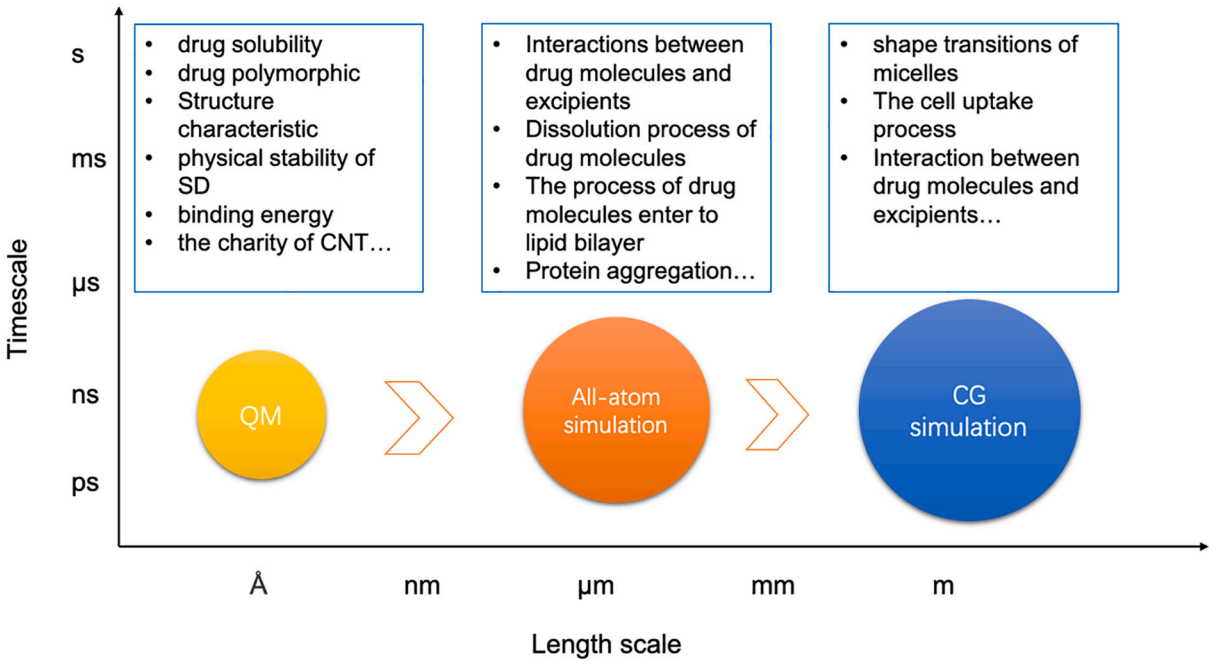


**Fig. 3.** Categories of molecular simulation methods and their applications in the pharmaceutical industry.

The energy change of sublimation is predicted by the QM method with the optPBE-vdW level of theory [57]. This approach has been validated against derivatives of benzoylphenylurea and benzodiazepine. More importantly, this approach shows the source of the low solubility of the molecule. For both drugs, lead optimization targeting reduced energy change of sublimation is more efficient than reducing that of hydration.

### *4.2. MD simulation and its application in pharmaceutics*

All-atom simulation is a traditional molecular dynamic (MD) simulation, wherein atoms are generally regarded as the smallest unit, which is based on the principles of Newtonian motion mechanics. The interaction between atoms is described by the empirical force field. According to the Boltzmann distribution law, the computer randomly assigns initial velocities to all atoms in the system, solves the equations of motion numerically to obtain the velocity and coordinate information at any moment, and then implements the simulation of macroscopic properties [58]. Relative to QM calculations, the interactions of electrons within atoms are ignored in MD simulation, which largely decreases the degree of freedom of the system. Although all-atom simulation cannot obtain the information about electronic interactions within atoms, this simplification can greatly increase the time and length scale of the simulated system, making MD simulation an effective method for calculating large system and macroscopic properties.

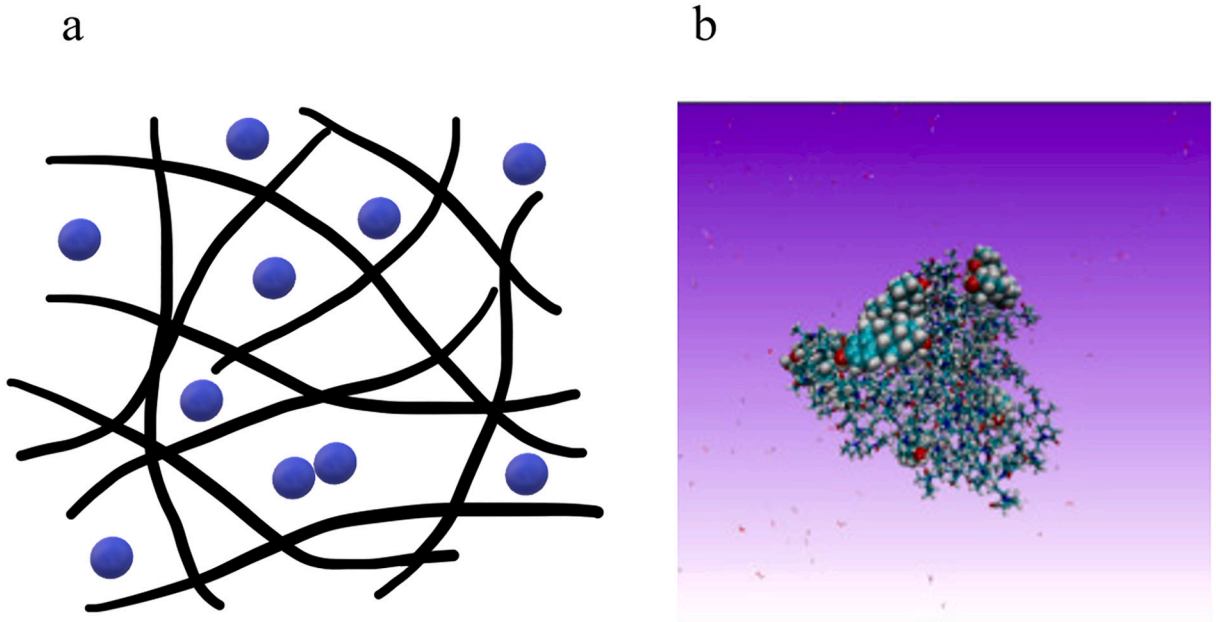


**Fig. 4.** (a), Traditional diagram of solid dispersion from reference; (b), the three-dimensional structure of solid dispersion in MD simulation from reference (Reprinted with permission from Han et al. [44]. Copyright (2019) Elsevier).

Recently, some studies investigated the preparation and dissolution process of solid dispersion formulations by MD simulation [59]. According to the traditional theory, drug molecules randomly disperse in the cavity of the network structure formed by the polymer chains, as shown in Fig. 4. Due to the high energy barrier of polymer network structures, amorphous drug molecules should be difficult to migrate and recrystallize, which is contrary to the aging phenomenon of a solid dispersion system [60]. Those MD simulation results showed that the linear polymer formed irregular coils under heating conditions and drug molecules adhered to the surface of the polymer irregular coils, as shown in Fig. 4(b) [44,61]. There were quite small voids in the coils of polymer, which was difficult to hold drug molecules. Drug molecules can easily move and aggerate to form crystals based on this theory, which better explains the physical instability of solid dispersion. Moreover, a study investigated the preparation and dissolution process of vemurafenib solid dispersion formulations by MD simulation [45]. In the preparation process, two solid dispersion formulations were formed using the annealing method. And then, the dissolution results showed that more vemurafenib molecules were released from the HPMCAS carrier than the Eudragit carrier, which corresponds to the experimental results. This may be caused by the HPMCAS polymer containing more hydrophilic groups than the Eudragit polymer.

The application of MD in CD inclusion technology is the fast-growing and the most effective field. The MD method is suitable to study the properties of the CD inclusion complex [62,63] and provide a theoretical basis for stable structures [64,65], diffusion coefficient [66,67], and chiral separation [68,69]. In our previous study, the effects of different types of CDs on the binding affinity of lutein were examined by Amber software [70]. Simulation results found that lutein molecules cannot insert into the α-CD cavity, while it can maintain a stable binding pose in β-CD, hydroxypropyl (HP)-β-CD, and γ-CD with the 1:1 ratio. Through calculating the binding free energy by MM-PBSA, they found that the van der Waals force was the highest contribution to the binding of lutein-CDs complexation. A similar method has also been applied to the study of andrographolide CD formulation, comparing the binding free energy of drug molecules to different types of CDs [71]. Another study combined the molecular docking and MD simulation methods to determine the dominant conformation of the candesartan-HP-β-CD binding pose [72].

Besides, MD has also been used in pharmaceutical studies of nucleic acid therapeutics. One early study investigated and compared the binding behavior of siRNA to polymers with four and eight positive charges [73]. The $4^{+}$ polymer is preferentially bound to the major groove of siRNA, and this system is easier to release siRNA since its lower binding free energy. The following study further simulated the saturated binding of polymers to siRNA at a high charge ratio, showing the quantified evidence of the binding capacity of the siRNA [74]. Uludag's group reported a lipid substituted polyethylenimine (PEI) for siRNA delivery. The simulation results showed that this delivery system did not affect the function of siRNA and the structure became more compact and stable [75]. Moreover, the lipid was located on the periphery of siRNA, which can enhance cell permeability and protect the siRNA from nuclease degradation. Additionally, Jasmin et al. used MD simulation and found that cationic cholesterol derivatives also was suitable to deliver DNA by ionic interactions [76]. Another study investigated the dynamic process of the combination of dendrimers with DNA [77]. This dendrimer is mainly located at the grooves of DNA, stabilizing the DNA structure.

### 4.3. CG modeling and its application in pharmaceutics

The all-atom simulation is still limitedly applied to large systems due to the massive computational calculation, and the time scale is only in the nanosecond range. For example, the shape transitions of micelles [78,79], the cell uptake process [80], as well as the interfacial diffusion behavior of surfactant molecules [81] are difficult to simulate using the traditional MD simulation method. Therefore, a CG model is designed to simplify the complex molecular interactions in a molecular system. The CG simulation is a further approximation to traditional all-atom MD simulation, greatly reducing the degrees of freedom of the system and improving the time scale of the simulated system to microsecond order of magnitude [82,83]. A study has developed a CG model to study the interaction between siRNA and cationic diblock copolymers, and the simulation results found that the length of the cationic block influenced the types of interaction [84]. In the latest research, Marrink et al. observed the release process of short fragments of double-stranded DNA from nanoscale liposomes using CG models [85]. When lipids fuse with the endosomal membrane, they form a pore that connects water channels to the inside of the cell, allowing DNA to escape. A CG model has been established to study the penetration mechanism of peptides [80]. When peptides were absorbed on the asymmetric membrane, it can cause the formation of hydrophilic pores in the membrane, thereby penetrating the cell membrane and reducing the membrane asymmetry.

## 5. Mathematical modeling

Limited by the computation efficiency, it is not feasible to calculate the dynamic change of a real system by considering the motion of every molecule involved. Thus, the behavior of the material in the macroscope needs to be described by mathematical equations. There are many mathematical models depicting the phenomenon resulted from the dissociation [86], association [87], fluxion [88], and collision [89] of a large number of molecules. The dissociation and association of molecules correspond to dissolution and precipitation or crystallization, respectively. Both of them are the basic issues of pharmaceutics since they influence the formulation bioavailability and manufacturing. More importantly, representation of both processes is the prerequisite for simulation about formulations' in vivo behavior, such as the PBPK modeling. Therefore, they will be introduced in this section, with some of their recent applications in pharmaceutics listed in Supplementary Table 3. Modeling methods for molecules fluxion and collision will be represented later.

### 5.1. Dissolution and release of drug

The process of dissolution and release is drug molecules depart from the formulation matrix into solution bulk. The Noyes–Whitney equation was the first model describing this process in 1897 [90]. Afterward, many other equations have been derived [91–93]. These equations are variant because the physical premises assumed for each equation are different, which are further dependent on the formulation types. Therefore, the key point of application is to choose a proper equation or model to describe the dissolution and release process in a real case.

In the simplest situation, the drug release can be described by Fick's law. That is, the dissolution is driven by diffusion along the direction of the drug concentration gradient or chemical potential gradient, irrespective of the liquid flow [94]. Fick's law is true if the formulation conforms to the following conditions: the formulation is diffusion-controlled; the diffusion coefficient of a drug is constant; perfect sink condition is true, and the polymer membrane outside the drug reservoir does not swell or dissolve throughout the release period; regardless of the geometry of particles [95]. The solution to Fick's law would result in a released amount proportional to the square of time, named Higuchi equation [96], which is often used to fit experimental data due to its simple form.

However, the Higuchi equation assumes the geometry is a thin film with negligible edge effects, which may not be holding true for all types of formulation. For drug particles in special shapes like spheres, thin-film, and cylinders, there are separately modified equations to increase the model accuracy [92]. Additionally, the diffusion coefficient in a real system is not necessarily maintaining a constant during the dissolution period. Some kinds of polymers resulting in the change of

drug diffusivity have been discussed [91]. One mechanism of diffusion change is that some drug molecules are adhering to polymers, impairing their release ability. Depending on whether the thermodynamic equilibrium between bound and free drugs is holding true, two models are optional [94].

Considering more complicated situations, when matrix contacts with release media, water goes into the matrix, and polymer also diffuses into water volume leading to polymer swelling or dissolution. Models considering polymer swelling could parameterize two diffusivities, one for drugs and one for polymer, respectively, with additional special edge conditions. Korsmeyer–Peppas model is one of such methods and successfully reproduces the release profile of (hydroxyethyl methacrylate-co-N-vinyl-2-pyrrolidone) copolymers-based films [97]. When considering polymer dissolution, a "sequential layer model" can be simulated, where the diffusion of water and drug release are both modeled with changing diffusivity. Another mechanism explaining polymer dissolution is reptation theory [98]. When water concentration at the surface exceeds a certain value, the polymer chains begin disentangling and diffuse into the release medium. This method has been proven useful to predict the drug release from HPMC-based formulation in a range of drug loading [99]. Further, the polymer may also degrade if polymer chains are cleaved into oligomers and monomers during release. In this situation, the formulation matrix can be divided into numerous elements with each element assigned a "lifetime expectancy", and the dissolution can be modeled by the Monte Carlo method. This approach successfully reproduced the release profile of 5-fluouracil from PLGA-based microparticles in phosphate buffer at pH 7.4 [100]. For formulations that show pore structure on their surface, the polymer degradation would alter the pore radius. The drug dissolution from such materials has been modeled by Tzur-Balter et al. [101], taking the degradable mesoporous Si thin films as an example.

In addition to calculating dissolution considering mechanism, the dissolution process can also be fitted to empirical or semi-empirical models. The Peppas equation [102] represents a release rate proportional to the power of time. The power is again dependent on the geometry of the formulation. Other empirical methods include the Hopfenberg model [103] and the Cooney model [104], both of them assume the release is to zero-order kinetic and can be adjusted according to particle shape. For non-polymer-based delivery systems, like lipid dosage form and liposome, the release model has been summarized in another latest review [93], which introduces release under the assumption that concentration gradient inside and outside liposomes is linear.

The models discussed above are based on the investigation of small molecules. However, recent studies have extended the release modeling methods to study large molecule therapeutics. In an intravitreal delivery system, a fusion protein of ciliary neurotrophic factor (CNTF) and Src homology 3 (SH3) is loaded in a hydrogel made from a physical blend of hyaluronan and methylcellulose. This blend is supposed to be injected into the vitreum as a controlled released delivery diffusing to the retina region in seven days [105]. The CNTF loading in the formulation is determined with the help of its release kinetics model [106]. This model incorporates the mechanism of protein equilibrium binding and determines affinity interaction strength, binding ligand concentration, dissociation rate, and hydrogel geometry and size as influencing factors. The experimental data shows this design is successful, and the pharmacology test indicates CNTF exerts a good effect.

Another example is the mathematical model in liposome formulation [107], which is PEGylated liposome loading doxorubicin HCl and further is connected to siRNA for producing gene-drug co-delivery system. This research has considered pH and temperature in the predicting model. First, the release profiles of doxorubicin-liposome in several release conditions were fitted to Peppas semi-empirical model: $release = k*t^n$ (t for time). K and n were further fitted with the variables are pH and temperature. The final model shows when the temperature is in the range of 25 and 42 °C and pH from 4 to 7.4, the R-square value is not less than 0.93, showing a good agreement between model and experimental data. This model is valuable because physiological or environmental conditions are limitedly considered in existing researches of modeling the release of liposomes. Models in the future may take more physicochemical properties into account when simulate drug release from liposomes.

### 5.2. Precipitation and crystallization of drugs

Basically, the crystallization process is suggested as two steps: nucleation and crystal growth [87,108]. Nucleation is the birth of a crystal when several solute molecules aggregate to form a crystal nucleus. Then more molecules precipitate on the surface of the nucleus to enlarge their size. The mathematical model for depicting nucleation can be categorized as mechanical or empirical. The mechanical model involves the computation of excess free energy of surface and volume between two phases. The Excess free energy of surface reflects the potential of the newly formed nucleus to redissolve, while excess free energy of volume indicates the tendency to condensation; their difference is a function of the nucleus's size, which determines a minimal radius necessary for nucleation where the propensity to redissolve and aggregate are equal. Energy combined with other properties like supersaturate solution activity and viscosity further defines the rate of nucleation. The empirical model of nucleation rate is in the form of a power function, where the power index stands for the number of molecules needed to form a nucleus [87,109]. For crystal growth, a classical explanation is the Gibbs-Volmer absorption layer theory [87], which describes the formation of a two-dimensional nucleus layer absorbed onto the existing crystal surface in thermodynamic equilibrium. This process asks for a critical minimal radius of the initial crystal and can calculate the critical excess free energy and the consequent growth rate. Other remaining models include the Burton-Cabrera-Frank (BCF) equation and the "birth and spread (B+S)" model [87]. Both of them provide models for the growth of the crystal layer on the surface. Proper choice of crystal growth model usually depends on alpha factor [110], which describes the crystal surface's roughness. BCF equation is suitable for a smooth surface, while the B + S model is applied to a rougher one.

From the thermodynamic perspective, crystals tend to aggregate to form larger particles to minimize the surface energy of the system. Thus, a crystal in a small size is prone to dissolve and re-crystallize on the surface of a bigger one. The Equation that depicts this transformation is called Ostwald ripening theory and has further been advanced by Lifshitz, Slyozof, and Wagner (LSW) [111]. Basic models contain one kinetic equation for the growth or reduction of an individual particle, one continuity equation for size distribution, and one mass conservation equation governing particle transformation.

Besides the above crystal growth mechanism, two particles, especially nanoparticles, can directly attach to each other to form a bigger particle, named the oriented attachment (OA) process. OA is significant at the primary stage of crystal growth because small misorientation of OA contributes to the dislocation, screw, and edges in crystals. Thus, many kinds of growth patterns, such as spiral growth, can occur [112]. The kinetic model for OA has been previously summarized [113]. Generally, equations for OA are similar to those for chemical reactions. Two small particles "react" at a rate constant to form bigger particles. What happens most frequently is the attachment of two primary particles to form a secondary particle. When a strong surface adsorbent is added into a system, particles at a higher level can integrate. The reaction rate constant for each level of reaction and particle concentration at each level can be computed by the Smoluchowski theory [114].

Since crystallization to some degree can be seen as a process where the particles in the second phase aggregate and separate but the total size maintains unchanged, the population balance (PB) equation is a promising modeling tool. The PB model has undergone a large development form that only defines the particle as a sphere to consider three-dimensional shape factors and growth rate variation on crystal faces

[115]. Recently, Rachah et al. [116] have used PB equations as a basic theory to design a continuous crystallizer with the removal of fine crystals and conducted a detailed mathematical analysis. However, the limitation of the PB model maybe its assumption that separates the nucleation process from Ostwald ripening. To handle this, Vetter et al. have tested a hybrid kinetic reaction rate equation, including nucleation, crystal growth, and Ostwald ripening [117]. A case study of the ADDoPT project [118] has tried to combine morphological PB with face-specific growth rate data to predict the evolution of crystallization and further achieve the digital design of and control the manufacturing process. This model successively captures the evolution of the shape and size and the distribution of ibuprofen crystals in seeded batch crystallizers.

The crystallization or precipitation can also be considered as the reverse of dissolution. Thus, the diffusion theory can also be used to simulate the precipitation [87]. This method is popular and convenient, especially for biopharmaceutics investigations, where dissolution and following precipitation are usually modeled together if needed. One example is the spring-and-parachute-like dissolution profile [119], commonly seen in the solid dispersion formulation, which consists of a rapid dissolution and a slow precipitation process. This pattern of dissolution can be modeled by using a time-dependent solubility determined by the maximal and eventual drug concentration and recrystallization rate constant. When the solubility gets less than the drug concentration at a certain time point, precipitation begins. This method has been proven to work well in amorphous temazepam formulation [120].

Last, regarding the crystal surface as a sum of discrete points, departure or attachment of a single molecule off or to each point can be seen as a probability issue. Thus, the crystal growth process could be modeled by Monte Carlo simulation, similar to the dissolution process. A recent detailed review has introduced how to apply such a method to handle surface kinetic problems [121]. The combination of Monte Carlo simulation and the first principle for electronic structure calculations seems to be a practical way to balance process modeling accuracy and efficiency.

## 6. Process simulation

The goal of the pharmaceutical industry is to produce stable and effective formulations. It is relatively easy to make a formulation with desired properties in the laboratory, but it will take more effort to manufacture qualified products on an industrial scale. The process simulation is a set of computational methods to control the quality of end products. So far, there are several good reviews about methodologies and applications of process simulation in the pharmaceutical industry [89,122,123]. In the present review, these methods are introduced as process analytical technology (PAT), computational fluid dynamics (CFD) modeling, and the discrete element method (DEM). Some additional case studies using these methods are listed in Supplementary Table 4.

### 6.1. PAT and its application in pharmaceutics

PAT strategy was early put forward in the FDA's guidance in 2004 [124] to encourage pharmaceutical producers to utilize innovative technology to improve product quality. PAT strategy emphasizes the process understanding and integrates engineering principles, pharmaceutical science, and quality assurance in manufacturing processes design. A desired PAT system can monitor the critical quality attributes during the manufacturing process and manipulates the production lines to make sure the product quality. PAT should be a critical technique in the newly raised manufacturing strategy “continuous manufacturing” [125], which highlights manufacturing from raw material to end product in a timely continuous manner. Currently, some measurement methods have been used in the PAT system. For example, near-infrared spectroscopy (NIR) [126] and focused beam reflectance measurement (FBRM) [127] could be used to detect particle size, and Raman spectroscopy can measure the homogeneity in formulations [128].

A PAT-based controlling system is introduced in the case study of crystallization to reduce the solvent content in crystals with bigger sizes [129]. This system is named the automated direct nucleation control (ADNC) approach. When the solute completely dissolves, the ADNC is initialized and cool down the system until crystalline nucleation forms. The number of nucleation is counted by the system, and when nucleation achieves the upper limit number, ADNC automatically heats the system to dissolve nucleation. Fig. 5 shows the crystallization control route of the ADNC system. Cycles of heating and cooling facilitate nucleation at a smaller size to dissolve and precipitate on the crystals' surface with a bigger size, eliminating the solvent in crystals and enlarging their size [130], which benefits the downstream processing.

One tablet continuous manufacturing line involves a PAT system, which receives the NIR spectra from detectors attached after bender and tablet press and controls the material feeding [131]. This system is developed basing on 460 spectra with various drug concentrations. After validation, this PAT equipment can detect the error in feeding materials and stop the manufacturing process instantly. One 28-h manufacturing test with this system produced tablets 100.86% ± 0.4% of label claim, showing the ability to control manufacturing accurately.

### 6.2. CFD modeling and its application in pharmaceutics

Generally, there are two strategies to conduct a dynamic simulation. Suppose the number of particles contented in the considered system is large enough. In that case, usage of the average parameter value of these particles can precisely depict the disposition of the system, and there is no need to calculate the interactions between individual particles. In order to handle this situation, some model equations of the continuum approach can be used. The CFD is such a method [122,123], using numerical analysis and data structures to study the motion of flowing media, like fluid, gases, or powders. The basic theory of fluid dynamics includes conservation equations of mass, momentum, and energy, as well as state equations. These equations define the rules that substance mass and speed at every point in the space of the system must conform to at any time.

In the pharmaceutical field, the CFD is often utilized in manufacturing process simulation to give understandings of underlying physical mechanics. First, CFD is usually used to investigate agitating processes, like mixing. A very recently published review [132] has

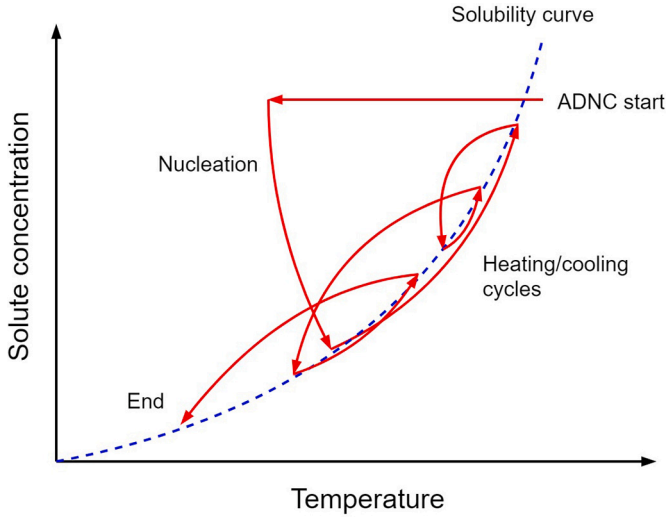


**Fig. 5.** The typical route of ADNC for controlling crystallization. (Redrawn from the article [129]).

discussed this topic in several aspects. The second situation involving CFD is granular material or powder flow. Models to handle this question were firstly referred to fluid or soil mechanics, then combined kinetic theory of gas shows [133]. CFD application in the granulation process has been introduced as one part of the review [123]. Besides, two other reviews have discussed CFD application to fluidized bed drying of wet porous granules [134] and many other drying equipment types [135].

Recently, there is an increasing interest in using CFD modeling to investigate the freeze-drying process. It can provide real-time information about the process where the flow visualization technique is difficult to apply in such low pressure. Alexeenko et al. [136] have used the CFD model to investigate the influence of the presence of clean in place (CIP)/sterilize in place (SIP) pipe in connecting duct on the velocity of flow. This model is for a manufacturing scale where the Knudsen number is low. Thus, the gas flow is in agreement with continuum flow and could be solved by Navier-Stokes equations that depict the equilibrium in mass, momentum, and energy. The modeling result is that despite the section area of the CIP/SIP pipe only takes a 3% proportion of the whole connecting duct, it decreases the velocity of flow in the duct by 20%, consistent with 22% as the experimental value. Recently, Barresi and Rasetto [137] and Marchisio et al. [138] introduced CFD modeling for lyophilization chamber, condenser duct, and valve. Authors have modeled multiple CFD results for freeze-drying equipment with different sizes, geometers, or configurations. Conclusions from these studies are profound because it gives clues about how to optimize apparatus design. For example, the connecting duct is suggested to be deployed at the bottom of the chamber to make pressure on plates more uniform even though this is at the cost of increased pressure. Besides, similar operating conditions would possibly result in different pressure on plates of various sizes. Higher pressure is observed on plates with a larger size.

Besides, CFD is a helpful tool for the development of inhalation formulation. An early review [122] has simply introduced some flow parameters that impact the drug amount achieving alveoli part, such as tumor size in the airway [139], as well as the mechanics of particle growth of inhaled formulation [140]. A later review specifically discussed how CFD is used to optimize the inhaler design [141].

One recent study has used the CFD model to find a critical parameter utilized in children's inhalation design [142]. The airway model is an idealized one that contains a mouth-throat and a trachea-bronchial tree changing as a function of age. Drug delivery systems of dry powder inhalers and nebulizer inhalers have been modeled. A dimensionless Stokes number has been used to characterize the disposition efficiency. The advantage of Stokes number is age independence. Stokes number at 0.06 and within the range of 0.03–0.04 indicates the dry powder inhaler and nebulizer inhaler achieve the highest disposition efficiency, respectively. This conclusion is useful for the development of inhalation for children. Besides, the commonly used human airway model for CFD does not consider the anonymous cartilage or ring-structure. However, this is improved in the newly developed Human Zygote5 model [143]. Validation of CFD modeling with Zygote5 airway against observed dispositional data of Budesonide from dry powder inhaler [144,145] shows a more consistent result than that from the traditional model. More disposition of drugs is observed in the Zygote5 model.

### 6.3. DEM and its application in pharmaceutics

If a flow cannot be considered a continuum flow, such as when the Knudsen number is large [136], CFD with Eulerian equations or Navier–Stokes equations will fail. In this case, DEM is more suitable. DEM is a Lagrangian model, which considers the interaction between elements by calculating the position, trajectory, and force burden of each unit and can address individual particle size distribution that cannot be processed in the continuum flow model [146]. Thus, DEM is beneficial and commonly used in powder or granular pharmaceutical formulation. The basic concept or theory of DEM and its application has been comprehensively reviewed by Yeom et al. [89] recently. Briefly, DEM is a process to calculate the force acting on each particle due to the collision, van der Waals interaction, liquid bridge, and electricity. Therefore, according to Newton's second law, update the position information in each time step.

So far, DEM has been used in many pharmaceutical processes, like milling, granulation, and coating, which have already been comprehensively reviewed [89]. In another common situation where a liquid is co-existing with particles in a system either by happenstance or by design, the liquid's influence requires DEM modeling to handle more demanding conditions. Zhang and Wu recently have developed a DEM model for wet particles, and the simulated result is consistent with the elastohydrodynamic model [147]. This study determines the Stokes number as a critical factor to influence rebound behavior. Further, an advanced CFD method, the lattice Boltzmann method, has been used with DEM to model the migration and aggregation of adhesive particles [148]. Other applications of CFD-DEM modeling to the processes of separation, comminution, filtration, and the processes in fluidized beds and bioreactors have also been very recently reviewed [88].

Except for the applications reviewed above, other processes like freeze-drying also involves the usage of DEM modeling [149]. The first step is randomly generating microparticles according to realistic particle size distribution. Then these microparticles are modeled to be thrown downwards and pile on the bottom of a vial. DEM models the collision between individual particles and calculates their motion. Following drying is modeled by the CFD model, and some packing properties like porosity, tortuosity, the average size of voids have been determined as related parameters to impact drying behavior.

## 7. Biopharmaceutical PBPK modeling

### 7.1. Introduction of PBPK modeling method

Drug dosage is hard to be taken up by the human body totally if not administrated via the intravenous route. Intrinsic exposure to the drug is important to assess the effect of formulations. Physiologically based pharmacokinetic (PBPK) modeling is a kind of PK prediction tool that can generally describe the concentration versus time profile in the body, which is the base to correlate to the therapeutic or toxic effect of drugs. The PBPK model structure comprises several compartments linked by differential equations, which indicates organs in the body connected to the circulating system. The parameters involved in the model are either related to drug physicochemical properties (molecular weight, lipophilicity, plasma unbound fraction, pKa, solubility, metabolism rate, etc.) or physiological properties (tissue volume, blood flow, vessel surface area, enzymes, and transporters expression, etc.) to calculate the PK profile [150]. Thus, the PBPK model is highly interpretable and easy to modify according to real conditions.

It is well accepted that the PBPK idea was first introduced in 1937 by Teorell [151], who used five compartments, including the circulatory system, kidney elimination, and drug pool, to simulate PK profile. After the development of nearly one century, the PBPK model is suitable to simulate the PK profiles for clinically pharmacological issues, such as special patient population and drug-drug interaction (DDI) situation, influencing the decision of dosage scheme [152]. Acceptance of simulated results by regulatory agencies in recent years intensively stimulates the PBPK application to the pharmaceutical industry [153].

With the development of the in vitro experiment methods, essential processes like drug formulation dissolution [86], distribution along the gastrointestinal [154], and absorption through the gut wall [155,156] can be parametrized and represented by mathematical models. This makes the simulation of the PK profile from basic formulation properties practicable, especially for oral drugs. The first integrated model structure that combines the processes above is the “compartmental absorption transit” (CAT) model [154], and its upgraded version, “advanced compartmental absorption transit” (ACAT) model (as shown in Fig. 6),

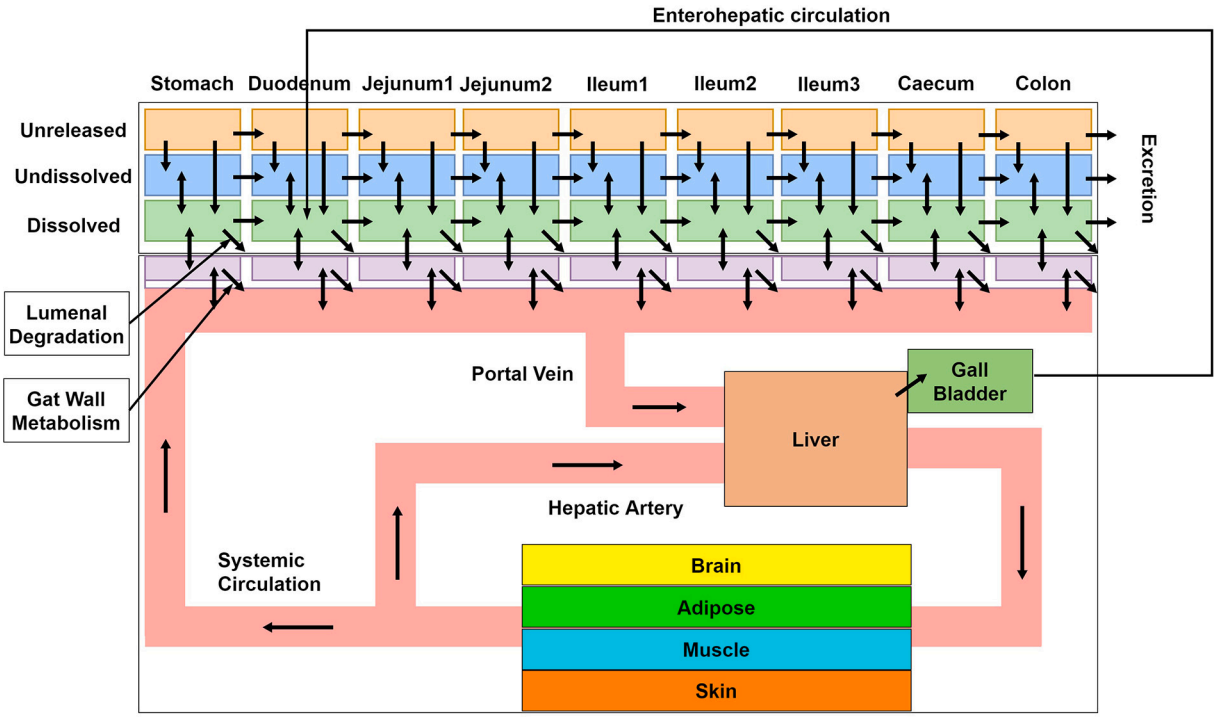


**Fig. 6.** The advanced compartmental absorption transit (ACAT) model. (Redrawn from the article [158]).

which was integrated into the following GastroPlus software (SimulationsPlus Inc.) in 1998 [157]. The first version can explain whether absorption or solubility/dissolution would be the limiting process in drug absorption, which is a huge advance for formulation development [158]. Besides GastroPlus, many PBPK software [159] are available at present.

In recent decades, PBPK has been increasingly used to study the intrinsic dug exposure depending on factors that pharmaceutical scientists concern about. This method has become an important tool in the MIDD approach, especially helping the generic drug development [21].

### 7.2. *Applications of PBPK modeling in pharmaceutics*

Solubilization methods are usually applied to improve the dissolution of poorly soluble drugs in the gastrointestinal tract to enhance their absorption. The PBPK method can be used to estimate the PK profile and assess the efficiency of newly developed formulations.

ASD is a solid-state formulation where active ingredients are dispersed in inactive carriers such as polymers rather than forming lattice structures [160]. Dispersion in polymers makes the drug concentration exceed its thermodynamic solubility and achieve a supersaturated state in solution [161], promoting drug absorption and bioavailability [162]. PBPK has been used in several studies to address the influence such as absorption site [163], crystal fraction [164] on the ASD formulation bioavailability.

In the case study [119] of reproducing the development route of vemurafenib ASD using integrated computational methods, the PBPK model (PK-Sim software, Open Systems Pharmacology), loaded the dissolution profile of ASD containing polymer HPMCAS, produces the plasma drug concentration curve in human that is close to the experimental result. The parameters other than dissolution profiles for building the ASD model were obtained either from open databases or by fitting to the PK profile of vemurafenib crystal form. The requirement about this prior knowledge should be reasonable when developing an ASD formulation. Application of PBPK could estimate the in vivo efficiency of newly developed ASD over the crystal form. As for the option of polymer HPMCAS, it could be suggested by the MD model predicting the dissolution process of ASD as mention above.

CD is another commonly used solubilization method. CD molecule has a hydrophobic interior space, capturing hydrophobic compounds and a hydrophilic exterior surface, facilitating dispersion of drugs among water. However, binding to CD, on the one hand, enhances the dissolution of the drug, but on the other hand decreases the free drug fraction that could be absorbed, which means the drug permeability through the gut wall is reduced. This trade-off has been primarily described with a mathematical model by Dahan et al. [165] Sun et al. [166] have used the PBPK model of GastroPlus to simulate PK profiles of progesterone formulated with the HP-β-CD at the molar ratio of 1:1, 1:3.44, and 1:10. Associated with the adjusted permeability, the formulation with the ratio of 1:3.44 shows the highest profile, consistent with the experimental data.

An improvement on the PBPK model for CD formulation has been made in one recent study [167]. This new PBPK model integrates the CD flow into the gastrointestinal tract in addition to the standard ACAT model (Fig. 7). By considering the CD concentration in the intestine, the CD-dependent drug solubility, free drug fraction, and permeability can be calculated in real-time. This model has been validated by the progesterone and andrographolide (AG) dataset. In the case study of AG [71], the γ-CD is suggested by AI or MD model to produce the formulation. The formulation dissolution profile, physicochemical and biopharmaceutical properties of AG, and the PK information are integrated to construct the PBPK model for AG-CD formulation. In this way, the PBPK method also estimates the in vivo efficiency of the new formulation.

3-D surface graph analysis [167] of the free drug fraction, a subsystem extracted from the PBPK model, quantitatively proves that the ratio of drug to CD corresponding to the slope determined in phase solubility tests induces the most absorption efficiency. Lower content of CD would result in precipitation in the intestine, while higher content of CD leads to impaired permeability. The advantage of this 3-D graph analysis is that it can be performed prior to the PBPK modeling, and it does not require parameters like permeability, making it easier to be used. The 3-D graph analysis also could infer the maximum plasma concentration, which is close to the experimental result.

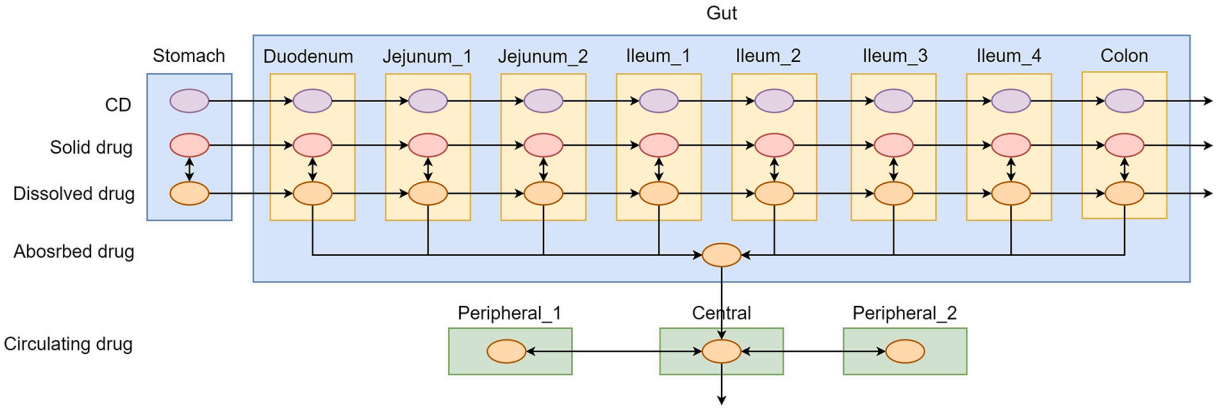


**Fig. 7.** Structure of newly developed PBPK model for cyclodextrin (CD) formulation (redrawn from the original article [167]).

Drug dissolution could also be enhanced by reducing the drug particle size [168]. This can be obtained by some mill processes like hammer mills, air-jet mills, and ball mills, which can produce particles smaller than ten μm [169]. More advanced techniques such as pearl milling, high-pressure homogenization, and controlled crystallization can produce particles at nano size [168]. The PBPK method has been used to assess the efficiency of drug particles manufactured to the size of both μm- [170,171] and nm- scale [172,173].

In the research investigating the relationship between the particle size and PK behavior of bitopertin [174], the size is parameterized into the Noyes-Whitney equation to describe the dissolution rate. The simulated in vivo dissolution profile is proven to be similar to the in vitro dissolution. The PBPK modeling result about drug plasma concentration has been validated by one study on monkeys and three studies on humans. After model validation, the parameter sensitivity analysis shows that the particle mean size smaller than 15 μm is expected to obtain both good $C_{max}$ and AUC. If a producer is limited by milling equipment, the size of larger particles (e.g., D90) should not exceed 30 μm to avoid unacceptable loss of $C_{max}$ and AUC.

Besides, other factors such as food effect [175,176] and precipitation [177,178] trend also impact the quality of formulation via influencing the dissolution process. Researchers from Novartis [179] also used the PBPK model to help the formulation development of one weak basic drug, NVS123, to alleviate the food effect on its bioavailability [180]. The Weibull equation has been used to describe the dissolution profile and adjust the equation's parameters to match the dissolution profile deconvoluted from observed plasma concentration-time profiles in the fed condition. Thus, an excellent IVIVC is established. This model also includes the precipitation time and the redissolution process since the drug precipitation is evident when the dissolution condition is changed from the gastric model to the intestinal model. The parameter sensitivity analysis (PSA) has been used to explore the impact of precipitation time and duodenum solubility on the fractional absorption of NVS123 in the fed condition and determine their values necessary for achieving a fractional absorption higher than 70%. According to the results, the amorphous formulation has been selected out, which is proven by the following experiment in dogs. Finally, virtual population simulation is conducted to further support the negative food effect on this form.

The PBPK method shows impressive successes in modeling the oral formulation. However, there are also many examples of applying the modeling method to more advanced and complicated formulations. In these cases, the model structures are often modified to simulate the real system.

The PBPK model for SNX-2112, an Hsp90 inhibitor in evaluation for cancer therapy [181], involves two sub-models representing the SNX-2112 nanoparticles and the non-particle drug molecules, respectively. The nanoparticles can be taken up into the liver and spleen by the mononuclear phagocytic system (MPS) like macrophagocytes [182], and they can release the non-particle drug in plasma, liver, and spleen, according to the release rate tested in vitro. Drug released behaves in a way that can be modeled by a standard PBPK model. The simulation result shows that although the elimination of nanoparticles by MPS is very rapid, SNX-2112 can immediately release from particles into the free drug, which prolongs its retention time.

An investigation about an mRNA therapeutic, hUGT1A1-modRNA, reports an associated pharmacokinetic/pharmacodynamic (PK/PD) model [183]. The mRNA is delivered via lipid nanoparticle (LNP), supplying the uridine-diphosphate-glucuronosyltransferase (UGT1A1) to treat Crigler Najjar syndrome type 1. The PK part is modeled by a classical compartment model, simulating the LNP elimination from plasma. The PD model simulates the endocytosis of LNP by liver hepatocytes, the release of mRNA from the endosome, translation of mRNA into UGT1A1, and the clearance of unconjugated bilirubin by UGT1A1, which is the biomarker of the disease. This model helps to find the proper dose for the first-in-human clinical study.

These examples (also listed in Supplementary Table 5) show that the PBPK method is a useful tool to assess the PK behaviors of drug formulation. For oral drugs, the PBPK model can predict the PK profiles benefited from the development of in vitro experimental methodology. For advanced drug formulations, though the construction of PBPK models often needs fitting to PK profiles obtained in the prior experiment [181,183], it still helps to improve our understanding of the formulation and suggest what we should do in the next step. For formulations given in other routes such as inhalation [184], transdermal agent [185], and eye drops [186], the PBPK models are also involved in research.

## 8. The future of computational pharmaceutics

### 8.1. *Prospective contribution of computational pharmaceutics*

"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 computer-aided method shifting the paradigm of drug design in the past three decades, computational methods also have great potential to change the approach of the pharmaceutical industry in the future.

On the one hand, computational pharmaceutics will promote the paradigm shift of drug delivery development. In the future, the QbD strategy [19] should be the mainstream adopted for the formulation design to guarantee product quality. QbD stresses the integration of process understanding into the design, which is definitely benefited from modeling methods. The AI model gives suggestions based on the principle underlying the data, and molecular modeling, PBPK, and mathematical modeling simulate the formulation behavior from multiple scales, supplying mechanical explanation to the in vitro and in vivo

process.

On the other hand, computational pharmaceutics will accelerate drug production. Future drug manufacturing should prefer the continuous manufacturing pipeline [187], which highlights the connection between producing units to avoid unnecessary exposure of the substance to the atmosphere and reduce the risk of error related to human manipulations. The continuous manufacturing relies on the PAT system, which can automatically supervise and control the production line during the process. Building a PAT system needs data science, requiring the AI method. The CFD and DEM method can simulate the manufacturing process, suppling process understanding about the PAT system.

The era that pharmaceutic is sufficiently supported by computational approach is expected as "Pharma 4.0" [188], where the drug and forms shall be in better design and the manufacturing process shall be digitized and automatically decided, performed, and controlled. As a result, the product with high quality shall be supplied to patients more efficiently.

### 8.2. The challenges and strategies to computational pharmaceutics

#### 8.2.1. Integration of multi-scale modeling

Currently, the studies in computational pharmaceutics commonly use just one of the computational methods and provide scattered information about formulation mechanisms. Integration of data sources of different stages is thought to promote pharmaceutical development [188]. However, integrating computational methods is very challenging for us.

Our two previous studies of the virtual design of vemurafenib ASD [119] and andrographolide CD [71] formulation prove that an integrated computational method is essential. In the two cases, AI and MD suggest the excipient category based on binding free energy or dissolution rate; the MD model further visualizes and analyses the interaction between drugs and excipient molecules; PBPK estimates the PK profile and assess the in vivo efficiency of the formulation. The validation against the experimental results indicates the virtual design route is acceptable and promising. This integrated method should promote formulation development in the future. The newly initialized NanoSolveIT Project also advocates dealing with the safety issue of nanomaterials by multi-scale modeling method [189].

The concept of the integrated computational method also includes a combination of different tools to deal with a single issue. There is a study that associates the ordinary differential equations of the PK/PD model with the neural network of AI algorithms to predict the response time course of patients receiving trastuzumab emtansine (T-DM1) treatment [190]. The predicted PD effect is more accurate than the "gold-standard" population PK/PD model. There are also some attempts to involve the AI algorithms in MD calculation [191,192]. This combination not only saves the computational cost but also enlarges the size limit of an MD task, which is in favor of the virtual screen of formulation on a large scale.

#### 8.2.2. Data challenges and opportunities

With the increasingly complex learning task, sufficiently huge and diverse data were required for model training. In practice, we were rarely able to find enough training data in individual institutions. A practical way to access more data is to collaborate with others, like taking part in cooperative projects such as OrBiTo and ADDoPT. However, data sharing faces great challenges of privacy and data ownership. A federated learning strategy can promote multi-institutional collaboration without sharing data. Federated learning utilizes multi-institutional data by distributed model-training. A 10-institutional federated learning results in the model performance as good as 99% of the model that is trained on aggregated data [193], superior to other collaborative learning approaches.

Another problem hindering data sharing is the heterogeneity in format or structure of different data sources [188,194,195]. A driving force from the regulatory agencies may promote the unification of data structure. KASA system, which is announced by FDA [20] recently to assess the product risk and quality, is data and algorithms based. Submitters to KASA may make their data compatible with the system.

#### 8.2.3. High-throughput and automatic experimental method

Computational pharmaceutical approaches also ask the way we produce data and validate against models to speed up. A high-throughput platform is one of the promising methods that perform a large number of experiments in a batch with high homogeneity [194,195]. The results of this method are with high credit to validate against those predicted data newly developed tools. This validation also helps to determine the boundary conditions of these models. Besides, an automatic robot would further enhance the experiment efficiency [196]. Linking the laboratory equipment [188] and experimental results [197] in one network can facilitate the process of data and reduce human error.

#### 8.2.4. Talent training and maintaining

Computational pharmaceutics counts on knowledge from both computational science and pharmaceutics. However, there is a big gap between pharmaceutical scientists and computational scientists. Current computational tools are still loosely connected to each other and are hard to be used by pharmaceutical scientists. A serious problem is the lack of talent with both computational and pharmaceutical backgrounds and experiences [194,195]. Initializing related education schemes covering undergraduate, postgraduate even Ph.D. periods is necessary to improve this situation. A new course, "Computational Pharmacy", was developed for the postgraduates at the University of Macau in 2015 and has achieved good student feedbacks. Besides, some stimuli are needed to promote people becoming experts in multi-discipline, such as funding and collaborative projects. However, this requires a change in culture in the pharmaceutical industry [188,194,195].

A platform where researchers can communicate with each other can also promote the development of computational pharmaceutics. Recently, the Computational Pharmacy Society was founded in November 2020. Furthermore, Computational Pharmaceutics became the first theme of the Asian Pharmaceutics Online Symposium (https://www.youtube.com/watch?v=kZr6RNbbiTk). These actions mark that this new interdisciplinary field has attracted more attention from pharmaceutical scientists and practitioners.

#### 8.2.5. Culture change in pharmaceutics

It is no doubt that traditional pharmaceutical development is highly costly, which asks for modern pharmaceutical companies to take a more efficient way to develop competitive products. Some researchers combine computational techniques with pharmaceutics and make progress. These investigations accelerate the development. Thus, the first understanding of computational pharmaceutics is to realize the substantial benefit brought about by computational pharmaceutics.

Second, computational techniques bring is not only about the profit on time or economy but also reveals more knowledge about pharmaceutics. Conventional pharmaceutical R&D is based on the trial-and-error method, and the decision is made according to empirical knowledge, leaving some basic questions unresolved. However, we cannot solve problems "at the same level we created them", and "a new type of thinking is essential if mankind is to survive and move to higher levels." [198]. Thus, we need computational methods in pharmaceutics. In1930, David Hilbert cited KANT's declaration in his famous speech, "*I maintain that in each particular natural science there is only as much true science as there is mathematics.*" Computational methods visualize the process, details how materials transfer and transform, and determines factors that significantly impact product quality. Knowing better about the process leads to safer and efficient formulations [19].

Third, we should realize that the industry paradigm shift cannot be accomplished in a short period. AI has not shown market relevance for

the core strategies of most leading pharmaceutical companies that already have applied AI technology at least until 2018 [26]. Therefore, it would be better to realize that involving computational techniques probably would cost considerable money and time but not produce a significantly observable profit in the near future. Historical materials typically tell that a successful revolution relies on long-term investment. During the First Industrial Revolution, the proportion of Britain's national income invested in purchasing long-lasting capital assets for future production was successively increasing for the whole period in that era [199]. Moreover, electricity, which is the symbol of the second industrial revolution, did not result in considerable growth in productivity until 1914–1917, the last stage of the Second Industrial Revolution, after major investments were dedicated to large central power plants and large-scale power transmission grids. Therefore, there was a long delay in the profit resulted from industry electrification [200]. Interestingly, this similar delay could also be seen in the early stage of the Third Industrial Revolution, where the productivity did not increase in parallel with the development of information technology, which has even led to a novel concept of "productivity paradox" [201] that has been debated until now. However, time has told how much the information revolution influences our modern life so far. The "productivity paradox" may be attributed to the difference in the financial nature between information and normal products or commodities, as early discussed by David [200,201]. The traditional "market-oriented indicators of productivity" may not be suitable to account for the value of information and data. The "productivity paradox" vividly represents the relationship between economic development and industrial evolution, just like the indispensable significance of the Financial Revolution for the First Industrial Revolution [202]. Therefore, from this perspective, a new quantitatively economic tool may be necessary to correctly describe the contribution of computational technology to the pharmaceutical industry. This development also helps to evaluate the work of multidisciplinary experts in companies and attract more talents into this area.

## 9. Conclusion

In the last decades, various computational methods have been involved in pharmaceutical researches. This present review summarizes applications including AI, molecular modeling, mathematical modeling, process simulation, and PBPK modeling. Computational methods should cut down the cost of pharmaceutical R&D by reducing the number of trial-and-error cycles and give us a deeper understanding of formulations. However, the computational methods in pharmaceutics so far are far from what is expected. The integrated method is desired for future computational pharmaceutics. To achieve this, several aspects need improvement. Data standardization and sharing, as well as the update of experiment and production facilities, are basically technical parts. The more important thing is to cultivate and maintain enough talents in this novel area. We should rightly understand the value of computational pharmaceutics, keep the faith, and have the patience to promote the paradigm shift until that Pharm 4.0 comes true.

## Declaration of Competing Interest

No competing interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2021.08.030.

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