International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 63-77 www.ijprajournal.com ISSN: 2249-7781

Computational Pharmaceutices-New Approach of Medicine Delivery

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Submitted: 03-03-2024 Accepted: 13-03-2024

ABSTRACT
Due to the longer time, greater cost and decreased productivity of novel molecular entities (NMEs).Pharmaceutics and drug delivery have assumed growing importance in the pharmaceutical business inrecentdecades.However contemporary formulation development still depends on time consuming, expensive and unpredictable classical trial and error studies.Inthe last ten years, a new field known as "computational pharmaceutics" has emerged in responseto the exponential growth of computing power and algorithms. This field integrates big data, artificial intelligence, and multi –scale modeling techniques into pharmaceutics, and has the potential of fundamentally alter the way the drugs are delivery to the patients. Pharmaceutical scientists can use multi-scale lenses provided by computational pharmaceutics to discloseinthe clinic includes revealing physical, chemical, mathematical, and data driven. Details ranging across pre-formulation studies, formulation screening, in-vivo prediction inthehumanbodyand precision medicine in the clinic.thecurrentstudiesoffersathroughandindepthoverviewofall aspects of computational pharmaceutics pharma 4.0 includingartificialintelligenceandmachine learning techniques , molecular modeling ,mathematical modeling , process simulation, and PBPK modeling. In addition to summarizing these technologies, theories and advancement, we also reviewed the legal requirements, existing difficulties, and potential future developments in the field, such as talent training and a cultural shift in the pharmaceutical sector.

Keyword: AI and machine learning,molecular modelling,process simulation,pbbk modelling and simulation in drug development,future of computational pharmaceutics.

COMPUTATIONAL PHARMACEUTICS

Arecent field of study called computational pharmaceutics with artificial intelligence and multi-scale modeling methods and it has the potential to fundamentally alter how formulations are developed. Todaycomputational pharmaceutics is able to provide multi-scale lenses to pharmaceutical scientists , reveling physical ,chemical, mathematical, and data driven details ranging across chemical stability ,polymorphism , formula screening and precision medicine computational approaches play a essential role in all areas of pharmaceutics , involving but not limitedtoquantummechanisms (QM) ,molecular dynamics simulation ,mathematical modeling , physiologically based pharmacokinetic (PBPK) modeling, process simulation , artificial intelligence (AI) , and machine learning algorithms .

By using Schrodinger equation quantum mechanics accurate description of electrons spatial positions, and other atomic and molecular scale things. It can forecast the physiochemical and structural characteristics of molecules under Newton rules of physics; molecular dynamics simulation stimulates the motion of atoms and molecules. The molecular mechanism of formulationbasedonmolecularmechanicsandtheempiricalforcefiledcanbeinvestigated usingmolecularmolding,whichcanalsobeexplorethestructural,dynamicandenergeticfeature of the medication and excipient .The numerical simulation of a physical process , such a production live is called process molding ,PBPK simulation can forecast how formulation will behave in terms of pharmacokinetic / pharmacodynamic (PK/PD) in humans.Largevolumesof accumulated experiments data can be cyed to develop a quantitative formulation prediction model using machine learning and AI algorithms to produced data-driven predictions. The development process can be

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genteelly accelerated by a well designedAIsystem,whichcanalso optimize formulations, reduce costs, maintain product consistency and collect and preserve the specialized knowledge and experience of formulation experts .Numerous significant grants and financing initiatives for computational pharmaceutics research have been announced globally in line with this trend. In a four year project, advanced digital design of pharmaceutical therapies aims to revolutionizetheUKpharmaceuticalbusinessbyenabl ingfuturedigitaldesignofwoven pharmaceutics tools OrBiTo , a 2012- launched contortion with 29 members from the academic and industrial worlds , intends to provide a framework for the logical use of predictive biopharmaceutics techniques for oral medication administration . In order to employ datasets effectively in the future, this study highlights PBPK and MD models as prediction tools and recommends using AI technology.

Since, this approach emphasizes the process understanding in product design, adhering to the pops strategy,regulatoryauthoritysuchastheFDAshouldex amineapplicationofcomputational approaches to pharmaceutics to promote the quality of the final product .Model informed drug development or model informed drug discovery and development .developnvx the FDA's and EMA'S favorable outlook in addition to the recently proposed methodologies. The Japanese pharmaceuticals and medical devices agency released a similar studuy in 2017. The centre for drug evaluation in china has been gathering recommendation for MIDD guidelines; these publications mostly etherize the use of PK modeling in medication development reviewing the current uses of various silicon tools in thepharmaceuticalfieldisnecessarytounderstandwhe re weneed to go because computational approaches are altering the drug R/D paradigm and the way of think.

AI and Machine learning

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". It was well recognized that pharmaceutical productdevelopmentisahigh dimensional optimization problem.

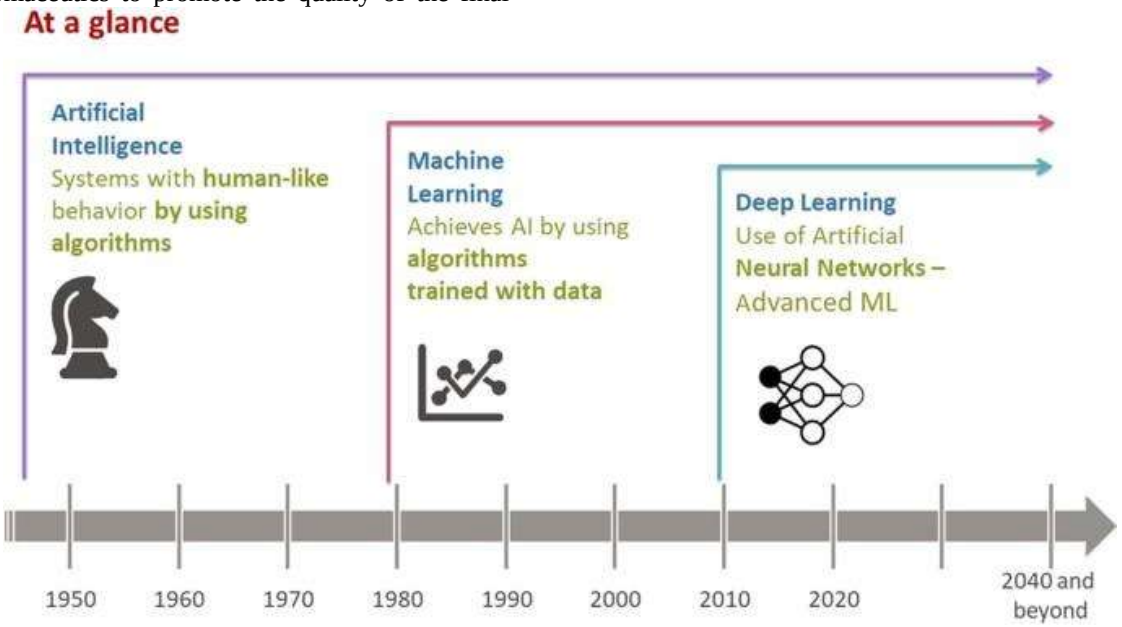

Figure num:1 At a glance

It is estimated that the size of the formulation space was around 1025–1030 (please refer to the Supplementary Information for calculation details). In such a high-dimensional space, it washard 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

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(AI), which can fit high-dimensional non-linear correlation based on big data and find the influence ofminorvarianceofinputsonthedifferenceoftargetedlabels.AIhasattractedalotof 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. AI is reported to be used in drug R&D at stages such asthedevelopmentofactivepharmaceuticalingredients(API),toxicologystudy,and clinical study, etc. Twenty-one leading pharmaceutical companies each have at least one application involving AI. This trend even has attracted tech giants like Google, Microsoft into medicine. Recently, the proteinstructurepredictiontoolAlphaFold2fromDeepMindshocksthe world with its experiment-level precision, showing the potential ofAIcombinedwithbiological 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 publishedby Ajaz S. Hussain and co-workers. An ANN model was trained to predict the drug release parameter, the dissolution half–time. Compared with the traditional response surface methodology,itwasshownthatANNhadhigheraccuracy,probablyduetothehigherdatafitting ability of ANN. Recently, with more cutting-edge algorithms occurring, such as deep neural networks(DNN),ensemblelearning,transferlearning, andsoon,AIhaspromotedtheR&D of numerous dosageforms,includingbutnotlimitedtohydrophilics ustained-releasematrixtablets, oral fast disintegrating film and tablets, cyclodextrin (CD) complex,amorphoussoliddispersion (ASD), nanocrystals, and so on.

Machinelearninginthecreationofformulations

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,invivopharmacokinetic(PK)parameters,drugdistribution, invivo-invitrocorrelation(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 dosageforms,includingASD,CDs,nanoparticles,self emulsifyingDDS (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 appliedmachinelearning methods to the prediction of the 3-month and 6 month physical stability of solid dispersion. 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,thedissolutionbehaviorsofsoliddispersionwere investigated bymachinelearning.The random forest algorithm was used to construct a classification model to distinguish two types of dissolution profiles of “spring-and-parachute” and “maintain super saturation” with 85% accuracy, 86% sensitivity, and 85% specificity in 5- fold cross-validation.

Therandomforestalgorithmwasusedtoconstructaregressionmodeltopredictthe time-dependent accumulative drug release with a mean absolute error of 7.78 in a 5-fold cross validation. CD complication enhanced the solubility of insoluble drugs and improved bioavailability and stability. CDs and guest drug molecules formed CD complication by the reversible binding. The binding free energy was a good indicator to estimate the bindingstrength. In 2019, the largest CD complication binding free energy dataset covering 3000 formulations were collected by Qianqian Zhao and co-workers. Eight types of CDs were included, and threemachinelearningalgorithmswereappliedandcompared.Theresultsshowed that the light GBM modeldemonstratedthebestperformanceof1.38kI/molmeanabsoluteerror. The feature importance obtained from light GBM 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.

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Various characteristics

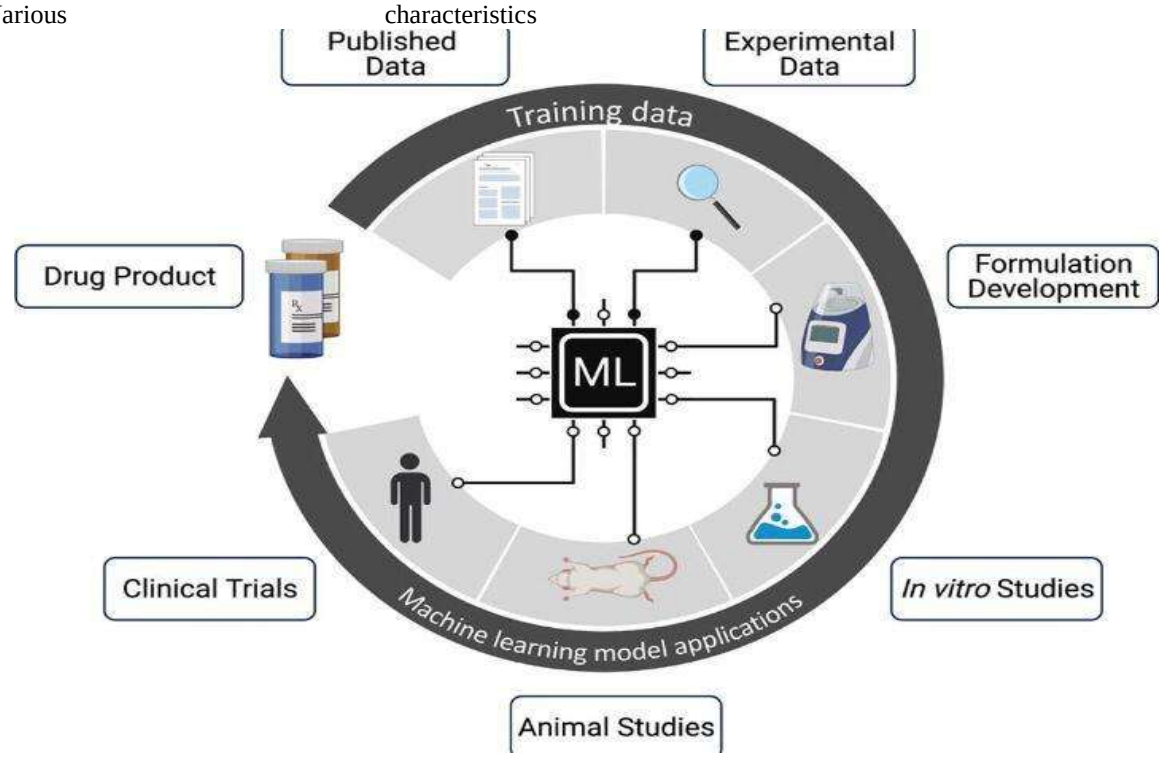

Figure num:2 Machine learning model applications

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 atthediseasesites.In2020,YuanHeandco-workersutilized machine learning techniques to predict nanocrystals. 910 particle size data and 310 PDI data coveredballwetmilling,highpressurehomogenization,andantisolventprecipitationmethods.

W. Wang et al. Journal of Controlled Release 338 (2021) 119–136 123 LightGBM models demonstratedgoodperformanceforthenanocrystalsproducedbyballwetmillingand high-pressure homogenization methods. The SEDDS were composed of oil, surfactant, cosurfactant, and APIs. The selection ofsuitableemulsifyingagentsandstabilizerswasacrucial step in the formulation development. In 2021, Haoshi Gao and coworkers collected a SEDDS dataset with 4495 formulation composition ratios. Sevenmachinelearningalgorithmswereused 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 accuraciesof91.3%accuracy,92.0%sensitivity,and90.7%specificityina5-fold cross-validation.ADOEmethodofcentralcompositedesign(CCD)wasusedtofurtherscreen

the ratios. In pharmaceutics, small data is a common problem in themachinelearningmodeling process. Transfer learning utilized the big data in the source domain and transferred the learned knowledge to thetargetdomainwithlimiteddatatoenhancetheperformance.Multitasklearning predicted the multiple tasks simultaneously and used the data of multiple tasks to learn the common network weights and knowledge. In 2019, an integratedtransferlearningandmultitask learning approachwasdevelopedtoconstructquantitativestructure-activityrelationship(QSAR) models for the prediction of the four human PK parameters by Zhuyifan Ye and co-workers. 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 withmore than 30 million entries. The integrated transfer learning and multitask learning approach was used to fine-tune

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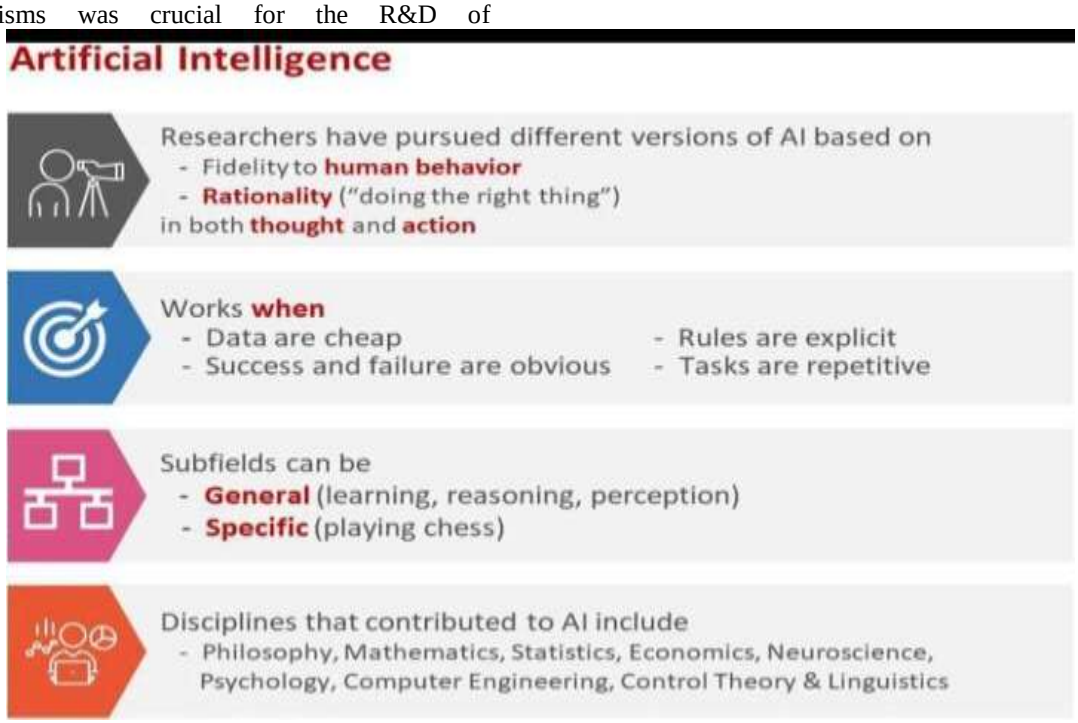
the model on the PK dataset. The results showed that the integrated approach enhanced the model generalizability. Model interpretability was increasingly consideredasimportantasmodelperformanceinformulationdevelopment.Thoughsome post-hoc interpretable methods have been proposed, methods based on post-hoc analysis faced the concern of faithfulness. In 2021, attention-based DNNs were proposed for pharmaceutical formulation development by Zhuyifan Ye and co-workers. 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 ofgreatsignificance,especiallygivensomeimplicitparameters.Generativemodels 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. 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

AIinprecisionmedicine

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, whichhadreflectedtheindividualizationofmedicaltreatmentsince ancient times.Frompersonalizedmedicinetoprecisionmedicine,ithasmanyimpactsondisease prevention, diagnosis, and treatment. As announcedbytheNationalInstituteofHealth(NIH),in precision medicine, the importance of factors of individual genes, environment and lifestyle is increasing.TheroleofAIinprecisionmedicineisindispensabletopredictwhichtreatmentisthe best for a patient.



We focused on the impact of AIinprecisionmedicineanddrugdelivery,takingtheright dose of insulin delivery for diabetes as an example. Patients with type 1 diabetes could be

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treated with insulin. The insulin pump is atypeofautomaticdrugdeliveryequipment.Thisauto maticinsulin 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 theirbloodglucose. This kind of healthcare achieved close monitoring, tailoring medicalinterventions,anddynamic modulation.
Applicationinleadoptimization.Ithasbeensuccessfull yadoptedtoselectoutthedrugmolecule Current problems of AI in pharmaceutics
The recent development of AI techniques has played anessentialroleintherationaldesignand development of pharmaceutical products. The successful application of many AI technologieshas shortened the development time, ensured the quality of products, and promoted thesuccessful R&D of pharmaceutical products. However, during applied machine learning algorithms,acommonproblemwaslackingdata.Thehi ghcostofpharmaceuticalexperiments

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.
Molecular modeling
According to the timescale and length scale, molecular modelingmainlycontainsthreedifferent parts:quantummechanics(QM),allatommoleculardy namics(MD)simulation,andcoarse-grained (CG) modeling. Their applications to pharmaceutical studies are listed in Supplementary.

QManditsapplicationsinpharmaceutics

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. In the development of PLGAcontaineddrugdeliverysystem,theQMmethod hasbeenusedtoanalyze the energy transition during the process of salted-out and PLGA cross linking, which involvesthe interaction between PLGA and N,N-dimethyl formamide (DMF) solvent, water, and hydrochloric acid (HCl). The simulation result for 26 formulations produces profiles of matrix resilience, energy absorbed, and mass deflection, which is consistent with the experimentalvalue. These results are important to judge the formulation stability when immersed in the phosphate-bufferedsaline solution. QM also shows the with the highest solubility from a series of similar compounds. 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.

The energy change ofsublimationispredictedbytheQMmethodwiththeo ptPBE-vdWlevelof theory. 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

MDsimulationanditsapplicationinpharmaceutics

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. Theinteractionbetweenatomsisdescribedbytheempir icalforcefield.Accordingto 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. 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

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information about electronic interactions within atoms, this simplificationcangreatlyincrease the time and length scale of the simulated system, making MD simulation an effective method for calculating large system and macroscopic properties.

Recently, some studies investigated the preparation and dissolution process of solid dispersion formulations by MD simulation. According to the traditional theory, drug molecules randomly disperse in the cavity of the network structure formed by the polymer chains. 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. Those MD simulation results showed that the linear polymer formed irregular coilsunder heating conditions and drug molecules adhered to the surface of the polymer irregular coils. There were quite small voids in the coils of polymer, which was difficult to hold drug molecules. Drug molecules can easily move and aggregate to formcrystalsbasedonthistheory, which better explains the physical instability of solid dispersion. Moreover, astudyinvestigated the preparation and dissolution process of vemurafenib solid dispersion formulations by MD simulation. 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 maybecausedbytheHPMCASpolymercontainingmorehydrophilic groupsthantheEudragitpolymer.TheapplicationofMD 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 and provide a theoretical basis for stable structures[64,65],diffusion coefficient and chiral separation . In our previous study, the effects of different typesofCDson the binding affinity of lutein were examined by Amber software. Simulation results found that luteinmoleculescannotinsertintotheα-CDcavity,whileitcanmaintainastablebindingposein β-CD, hydroxypropyl (HP)-β-CD, and γ-CD with the 1:1 ratio. Through calculating thebinding free energy by MM-PBSA, they found that the van derWaalsforcewasthehighestcontribution tothe binding of lutein-CDs complication. A similar method has also been applied to the studyof andrographolide CD formulation, comparing the binding free energy of drug molecules to different types of CDs. Another study combined the molecular docking and MD simulation methodstodeterminethedominantconformationofthe candesartan-HP-β-CDbindingpose.

Besides, MDhasalsobeenusedinpharmaceuticalstudiesofnucleicacidtherapeutics.Oneearly study investigated and compared the bindingbehaviorofsiRNAtopolymerswithfourandeight positive charges. The 4+ polymer is preferentiallyboundtothemajorgrooveofsiRNA,andthis systemiseasiertoreleasesiRNAsinceitslowerbinding freeenergy.Thefollowingstudyfurther simulated the saturated binding of polymers to siRNA at a high charge ratio, showing the quantified evidence of the binding capacity of the siRNA. Uludag's group reported a lipid substituted polyethylenimine (PEI) for siRNA delivery. The simulation results showed that this delivery systemdidnotaffectthefunctionofsiRNAandthestructurebecamemorecompactand stable. Moreover, the lipid was located on the periphery of siRNA, which can enhance cell permeability and protect the siRNA from nuclease degradation. Additionally, Jasmin used MD simulation and found that a cationic cholesterol derivative also was suitable to deliver DNA by ionic interactions. Another study investigated the dynamic process of the combination of dendrite's with DNA. This dendrite is mainly located at the grooves of DNA, stabilizing the DNA structure.

CGmodelinganditsapplicationinpharmaceutics

The all- to large systems due to the massive computational atom simulation is still limitedly applied calculation, and the time scale is only in the nanosecond range. For example, the shape transitions of micelles, the cell uptake process, as well as the interfacial diffusion behavior of surfactant molecule are difficult to simulate using the traditional MD simulation method. Therefore, aCGmodelisdesignedtosimplifythecomplexmolecularinteractionsinamolecular 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. A study has developed a CG model to study the interaction

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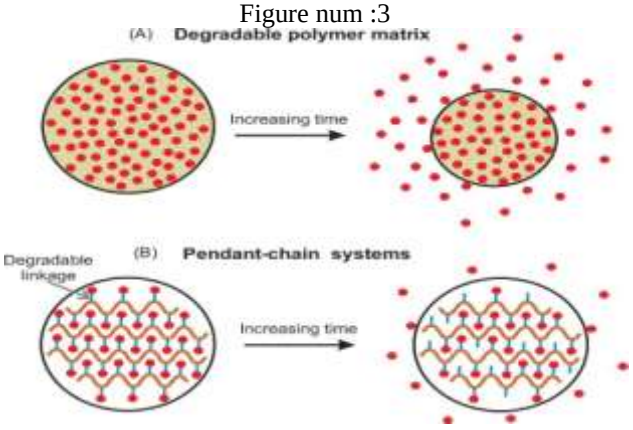
between siRNA and cationic dib lock copolymers, and the simulationresults found that the length ofthecationicblockinfluencedthetypesofinteraction.In thelatest research, Marrinketal.observedthereleaseprocessofshortfragmentsofdouble-strandedDNA from nanoscale leptosomes using CG models. When lipids fuse with the endosomal membrane, they form a pore that connects water channels to the insideofthecell,allowingDNAtoescape. A CG model has been established to study the penetration mechanism of peptides. Whenpeptides were absorbed on the asymmetric membrane, it can cause the formationofhydrophilic pores in the membrane, thereby penetrating the cell membrane and reducing the membrane asymmetry.

Precipitationandcrystallizationofdrugs

Basically, the crystallization process is suggested as two steps: nucleation and crystal growth. Nucleation is the birth of a crystal when several solute molecules aggregate to form a crystal nucleus. Then more molecules precipitate on the surfaceofthenucleustoenlargetheirsize.The mathematicalmodelfordepictingnucleationcan be categorized as mechanical or empirical. The mechanical model involves the computation of excess free energy of surface and volumebetween two phases.TheExcessfreeenergyofsurfacereflectsthepotentialofthenewlyformed nucleus to rediscover, while excess free energy of volume indicates the tendency tocondensation; their difference is a function of the nucleus's size, which determines a minimal radius necessary for nucleation where the propensity to rediscover 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. For crystal growth, a classical explanation is the Gibbs-Volker absorption layer theory, 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. Both of them provide models for the growth of the crystal layer on the surface. Proper choice of crystal growth model usuallydependsonalphafactor,whichdescribes 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 toformlargerparticlestominimizethesurfaceenergyofthesystem.Thus,acrystalin 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 hasfurtherbeenadvanced by Lifshitz, Slyozof, and Wagner (LSW). 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 primarystage of crystal growth because small disorientation of OA contributes to the dissolution.

Figure num :3



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Screw , and edges in crystals. Thus, many kinds of growth patterns, such as spiral growth, can occur. The kinetic model for OA has been previously summarized. Generally, equations forOA are similar to those for chemical reactions. Two small particles"react"atarateconstanttoform bigger particles. What happens most frequently is the attachment of two primary particles toform a secondary particle. When a strong surface adsorbent isaddedintoasystem,particlesata higher level can integrate. The reaction rate constant for each level of reaction and particle concentrationateachlevel can be computed by the Smoluchowski theory. 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 W. Wangetal.JournalofControlledRelease338(2021)11 9–136127. Recently, have used PB equations as a basic theory to design a continuous crystallizer with the removal of fine crystals andconductedadetailedmathematicalanalysis.Howe ver,thelimitation of the PB models 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 Ostwaldripening.AcasestudyoftheADDoptproject 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 successivelycapturestheevolutionoftheshapeandsize 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 diffusiontheorycan also be used to simulate the precipitation. This method is popularandconvenient,especiallyfor biopharmaceutics investigations, where dissolution and following precipitation are usually modeled together if needed. One example is the spring-and-parachute-like dissolution profile, commonly seen in the solid dispersion formulation, which consists of a rapid dissolution and a slow precipitation process.Thispatternofdissolutioncanbemodeledbyus ingatime-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. Last, regarding the crystal surface as a sum of discrete points, departure or attachment of a single molecule off or to each point canbeseenasaprobabilityissue.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. 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.

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.Theprocesssimulationisa setofcomputationalmethodstocontrol the quality of end products. So far, there are several good reviews about methodologies and applications of process simulation inthepharmaceutical industry. In the present review, these methods are introduced as process analytical technology (PAT), computational fluid dynamics (CFD) modeling, and thediscreteelementmethod(DEM). Some additional case studies using these methods are listed in Supplementary Table 4.

PATanditsapplicationinpharmaceutics

PAT strategy was early put forward intheFDA'sguidancein2004toencouragepharmaceut ical 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 theproductionlines to make sure the product quality. PAT should be a critical technique in the newly raised manufacturing strategy "continuous manufacturing" 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

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example, near-infrared spectroscopy (NIR) and focused beam reflectance measurement (FBRM) could be used to detect particle size, and Raman spectroscopy can measure the homogeneity in formulations. A PAT-based controlling system is introducedin the case study of crystallization to reduce the solvent content in crystals with bigger sizes. 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 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 crystalsandenlargingtheirsize,whichbenefitsthe downstream processing. One tabletcontinuousmanufacturinglineinvolvesaPATsystem,which receives the NIR spectra from detectors attached after bender and tablet press and controls the material feeding. This system is developed basing on 460 spectra with various drug concentrations. After validation,thisPATequipmentcandetecttheerrorinfeedingmaterialsand stop the manufacturing processinstantly.One28-hmanufacturingtestwiththissystemproduced tablets 100.86% ± 0.4% of label claim, showing the ability to control manufacturing accurate.

CFDmodelinganditsapplicationinpharmaceutics

Generally, there are two strategies to conduct a dynamic simulation. Suppose the number of particlescontentedintheconsideredsystemislargeenough.Inthatcase,usageoftheaverage parameter value of these particles can precisely depict the dispositionofthesystem,andthereis no need to calculate the interactions between individual particles. In order to handle thissituation, some model equations of the continuum approach can be used. The CFD is such a method , using numerical analysis and data structurestostudythemotionofflowingmedia,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 thespaceofthesystemmustconformtoatanytime. Inthepharmaceuticalfield,theCFDisoftenutilizedinmanufacturingprocesssimulationtogive understandings of underlying physical mechanics. First, CFD is usually used to investigate agitating processes,likemixing.Averyrecentlypublishedreview.ThetypicalrouteofADNC for controllingcrystallization. (Redrawn from the article. W. Wangi Journal of Controlled Release 338 (2021) 119–136 128 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, and then combined kinetic theory of gas shows. CFD application inthegranulationprocesshasbeenintroducedasonepartofthereview.Besides,two otherreviewshavediscussedCFDapplicationtofluidizedbeddryingofwetporousgranulesand many other drying equipment types. Recently, there is an increasing interest in using CFD modeling to investigate the freeze-drying process. Itcanprovidereal-timeinformationaboutthe process where the flow visualization technique is difficult to apply in such low pressure. Alexeenko. have used the CFD model to investigate the influence of the presence of clean in place (CIP)/sterilize in place (SIP) pipe inconnectingductonthevelocityofflow.Thismodelis for a manufacturing scale where the Knudsen number is low. Thus, thegasflowisinagreement with continuum flow and couldbesolvedbyNavier-Stokesequationsthatdepictthеequilibrium 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,itdecreasesthevelocity of flow intheductby20%,consistentwith22%astheexperimentalvalue.Recently,Barresiand Rasetto and Marchisio. 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 howtooptimizeapparatusdesign.Forexample,theconnectingduct 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 ofvarioussizes.Higherpressure is observed on plates with a larger size. Besides, CFD

International Journal of Pharmaceutical Research and Applications
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is a helpful tool for the development of inhalation formulation. An earlyreviewhassimplyintroducedsomeflowparameters thatimpact the drug amount achieving alveoli part, such as tumor size in the airway, as well as themechanics of particle growth of inhaled formulation. A later review specifically discussed how CFD is used to optimize the inhaler design. One recent study has used the CFD modeltofinda critical parameter utilized in children's inhalation design. The airway model is an idealized one thatcontainsamouth-throatandatrachea-bronchialtreechangingasafunctionofage.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 ageindependence.Stokesnumberat0.06andwithinthe rangeof 0.03–0.04 indicates the dry powder inhaler and nebulizer inhaler achievethehighestdisposition efficiency, respectively. This conclusion is useful for the developmentofinhalationforchildren. 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. Validation of CFD modeling with Zygote5 airway against observed dispositional dataof Budesonidefromdrypowderinhalershowsamoreconsistentresultthanthatfromthetraditional model. More dispositions of drugs are observed in the Zygote5 model.

If a flow cannot be considered a continuum flow, such as when the Knudsen number is large, 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.Thus,DEMis 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. 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 alreadybeencomprehensivelyreviewed.Inanothercommonsituationwherealiquidis co-existing with particles in a system either by happenstance or by design,theliquid'sinfluence 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. 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. Other applications of CFD-DEM modeling to the processes of separation, combination, filtration, and the processes influidizedbedsandbioreactorshavealsobeenveryrecentlyreviewed.Exceptfor the applications reviewed above, other processes like freeze-drying also involves the usage of DEM modeling. The first step is randomly generating micro particles according to realistic particle size distribution. Then these micro particles 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.

PBPK Modeling & Simulation in Drug Development

WhatisPBPKModeling&Simulation?

Physiological based pharmacokinetic modeling and simulation (PBPK) is a computer modelingapproachthatincorporatesbloodflowandtissuecomposition of organs to define the pharmacokinetics(PK)ofdrugs.TheconceptofPBPK was first described by Teorell in 1U37. Simply put, PBPK is a tool to assess factors responsible for patient variability that impacts the PK of drugs. Alterations in PK properties, such as, absorption, distribution, metabolism, and excretion (ADME), can have a substantial impact on achieving the desired therapeutic concentration of a drug. Too low of a concentration results in ineffective therapy, and too high may result in side effects or even toxicity. PBPK is a powerful tool that requires modern computational power to handle the intense and complicated mathematical equations necessary

International Journal of Pharmaceutical Research and Applications
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to make quantitative PK estimations and predictions. PBPK provides a mechanistic approachtostudyandpredictthePKof drugs based on physiologic and anatomic characteristics, as well as the physical and chemical properties of a given drug. The goal of any drug or therapeutic intervention is to be effective without causing harm. Depending on the drug and the individual taking it, this canbeadifficulttask;nonetheless,thisisanessential and actionable area for translational science. The utilization of intelligent PBPK models and simulations presents countless opportunities for improvements in drug development.

Methodology&ComponentsofaPBPKModel

Non-compartmental analysis (NCA) is a standard PK modeling tool. NCA is an empirical model that lacks physiological meaning. NCA assumes that the dose administered is distributed uniformly throughout the body and that the elimination of the drug is defined through a rate constant that does not account for physiology. This modeling approach allows for rapid generation of PK parameter estimates but does not account for any physiological mechanisms or biological processes that drive or alter PK. Population pharmacokinetic analysis (PBPK)isanotherstandardtooltodescribethePKofadrug.Typically,population PK models are empiric as well but can also be semi-mechanistic. Alternatively, a PBPK model is**based**on physiology, biological processes, organ function, enzyme/transporter abundance and function, andbloodflow,etc.PBPKmodeling andsimulationincorporatesphysiologicallydrivenparametersetsthatareresponsible for PK variability among patients. The PBPK model allows us to include:

- Physic-chemicalpropertiesofthedrug
- Specificphysiological differences
- TrialdesigninformationApopulationcanbedefinedasnearlyanygroupof people or clinical scenario such as:
- Healthypatients
- Patientswithatumorordiseasethataffectsoralters organfunction
- Lifeevent/stage(childhood,pregnancy,orpost-surgerypatients)

The patient'scharacteristics(age,sex,weight,bodycomposition,organfunction, genetics, etc.), can also be utilized and integrated in a PBPK model. The drug properties used in PBPK models include molecular weight, log P, p Ka, protein binding data, blood/plasma ratio, metabolism, permeability/solubility, transport mechanism,lipophilicity,etc.Themodelthencanpredi ctthePKofadrugbeforea study is conducted and the study can then be used to verify the prediction. Each cycleofpredictionandverification-fromanimal→healthysubjects'→topatient
*to special population - is accomplished by changing the physiological parameters within the model. Regulatory agencies have begun to accept PBPK modeling in place of many drug-drug interactions (DDI), pediatric, special populationstudiesandmore.PBPKmodelingcanalsobereferredtoas bottom-up or mechanistic modeling and simulation.

BenefitsandApplicationsofUsingPBPKModels

The benefit of using PBPK modeling is that it is a cost-effective and robust predictivetoolthatisdevoidoftheethicalchallengesassociatedwithclinicaltrials in sensitive populations (e.g. cancer patients, pediatrics, pregnant women, etc.). The physiological effects that alter PK are vast and, in some cases, they are compounding. There is a critical need for PBPK investigation, especially for drugs with a narrow therapeutic window and sensitive patient populations. For example, applications can include pregnancy populations, organ transplant populations, and bariatric surgery patients

PBPKLimitations

PBPK models utilize assumptions about the rates of each individual process and sometimes these rates may be unknown.Inthesecases,sensitivityanalysescan be undertaken to understandtheconsequencesofuncertainty.Anotherlimitation is that PBPK models tend to describe the average person with a disease of interest but does not describe inter-individual variability and unexplained variability(incontrasttopopulationPKmodeling).Thislimitationcanbe

overcome by sensitivity analyses with high and low values for important characteristics.
The future of computational pharmaceutics

Prospectivecontributionofcomputationalpharmaceutics

International Journal of Pharmaceutical Research and Applications
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"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-aidedmethodshifting 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 QbDstrategy should be the mainstream adopted for the formulation design to guarantee product quality. QbD stresses the integrationofprocessunderstandingintothedesign, which is definitely benefited from modeling methods. The AI modelgivessuggestionsbasedon the principle underlying the data, and molecular modeling, PBPK, and mathematical modeling simulate the formulation behavior from multiplescales,supplyingmechanicalexplanationtoth e in vitro and in vivo. Structure of newlydeveloped PBPK model forcyclodextrin (CD) formulation(redrawnfromtheoriginalarticle).W.Wan getal.JournalofControlledRelease338 (2021) 119–136 131 process. On the other hand, computational pharmaceutics will accelerate drug production. Future drug manufacturing should prefer the continuous manufacturingpipeline, which highlights the connection between producing units to avoid unnecessaryexposure of the substance to the atmosphere and reduce the risk of error related to human manipulations. The continuousmanufacturingreliesonthePATsystem,wh ichcanautomatically 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, supplying process understanding about the PAT system. The era that pharmaceutics is sufficiently supported by computationalapproachisexpectedas"Parma4.0"wh erethedrugand forms shall be in better design and the manufacturing process shall be digitized andautomatically decided, performed, and controlled.Asaresult,theproductwithhighqualityshal l be supplied to patients more efficiently.

Data challenges and opportunities with the increasingly complexlearningtask,sufficientlyhuge anddiversedatawererequiredformodeltraining.Inpra ctice,wewererarelyabletofindenough training data in individual institutions. A practicalwaytoaccessmoredataistocollaboratewith others, like taking part in cooperative projectssuch as OrBiTo and ADD opt. 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 inthe model performance as good as 99% of the model thatistrainedonaggregateddata,superior to other collaborative learning approaches. Another problem hindering data sharing is the heterogeneity informatorstructureofdifferentdatasources[188,194, 195].Adrivingforcefrom the regulatory agencies may promote the unification of data structure. KASA system, which is announced by FDArecentlytoassesstheproductriskandquality,isdat aandalgorithmsbased. Submitters to KASA may make their data compatible with the system. High-throughput and automaticexperimentalmethodComputationalpharm aceuticalapproachesalsoaskthewaywe

produce data and validate against models to speed up. A high throughput platform is one ofthe promising methods that perform a large number of experiments in a batch with high homogeneity. 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. Linking the laboratory equipment and experimental results in one network can facilitate the process of data and reduce human error.

Talenttrainingandmaintaining

Computational pharmaceutics counts on knowledge from both computational science and pharmaceutics. However, there isabiggapbetweenpharmaceuticalscientistsandcomp utational scientists. Currentcomputationaltoolsarestillloselyconnectedt oeachotherandarehardtobe used by pharmaceutical scientists. A serious problem is the lack of talent with bothcomputational and pharmaceutical backgrounds and experiences. Initializing related education schemes covering undergraduate, postgraduate even Ph.D. periods is necessary to improve this situation. A new course, "Computational Pharmacy", was developedforthepostgraduatesatthe UniversityofMacauin2015andhasachievedgoodstud entfeedbacks.Besides,somestimuliare needed to promote people becoming experts in multi-

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 63-77 www.ijprajournal.com ISSN: 2249-7781

discipline, such as funding and collaborative projects. However, this requires a changeinculture inthepharmaceuticalindustry. 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. These actions mark that this new interdisciplinary field has attracted more attention from pharmaceutical scientists and practitioners.

Culturechangeinpharmaceutics

It is no doubt that traditional pharmaceutical development is highly costly, which asks for modern pharmaceutical companies to takeamoreefficientwaytodevelopcompetitiveproducts. Some researchers combine computational techniques with pharmaceutics and make progress. These investigations accelerate the development. Thus, the first understanding ofcomputational pharmaceuticsistorealizethesubstantialbenefitbroughtaboutbycomputationalpharmaceutics. Second, computational techniques bring is not onlyabouttheprofitontimeoreconomybutalso reveals more knowledge about pharmaceutics. Conventional pharmaceutical R&D is based onthe 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. Thus, we need computational methods in pharmaceutics. In1930, David Hilbert cited KANT's declaration in his famous speech, "I maintain that in each particular naturalscience there is only as much true science as there is mathematics." Computational methods visualize the process, details how materials transfer and transform, and determine factors that significantlyimpactproductquality.Knowingbetteraboutheprocessleadstosaferandefficient formulations.Third,weshouldrealize that the industry paradigm shift cannot be accomplished inashortperiod.AIhasnotshownmarketrelevancefor W.Wangetal.JournalofControlled

Release 338 (2021) 119–136 132 the core strategies of most leading pharmaceutical companies that already have applied AI technology at least until 2018. 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 IndustrialRevolution,theproportionofBritain'snationalincomeinvestedinpurchasing long-lasting capital assets for futureproductionwassuccessivelyincreasingforthewholeperiod in that era. Moreover, electricity, whichisthesymbolofthesecondindustrialrevolution,didnot 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 resultedfrom industry electrification.
Interestingly,thissimilardelaycouldalsobeseeninthee arlystage 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" that has been debated until now. However, time has told how much the information revolution influences our modern life sofar.The"productivityparadox"maybeattributedtothe difference in the financial nature between information and normal products or commodities, as early discussed by David. The traditional "market-oriented indicators of productivity" may notbe suitable to account for the value of information and data. The"productivityparadox"vividly represents the relationship between economic development and industrialevolution,justlikethe indispensable significance of the Financial Revolution for the First Industrial Revolution. 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 expertsincompaniesand attract more talents into this area

CONCLUSION

Pharmaceuticals research has utilized a variety of computational pharmaceutical techniques in recent years. The application converted in this most recent assessment including A.I, PBPK molding ,Mathematical molding ,Process

International Journal of Pharmaceutical Research and Applications
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simulation, Molecular modeling .By lowering the number of trial and error cycles and providing a better knowledge of formulations , computational approaches should lower the cost of pharmaceuticals R/D . But pharmaceutical's computational techniques are far from what is anticipated. For upcoming computational pharmaceutics, an integrated approach is proffered. The many factors must be improved in order to achieve this modernization of experiment and production facilities, as well as data standardization and sharing are essentially technical components. The most crucial factor is to develop and preserve enough talent in this unique field. In order to successfully advance the paradigm shift and bring about pharma 4.0, we must currently appreciate the importance of computational pharmaceutics, Maintain our trust ,and exercise patience.

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