

Artificial Intelligence in Pharmaceutical Technology and Drug Delivery System

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Abstract: *Artificial Intelligence (AI) focuses in producing intelligent modelling, which helps in imagining knowledge, cracking problems and decision making. Recently, AI plays an important role in various fields of pharmacy like drug discovery, drug delivery formulation development, polypharmacology, hospital pharmacy, etc. In drug discovery and drug delivery formulation development, various Artificial Neural Networks (ANNs) like Deep Neural Networks (DNNs) or Recurrent Neural Networks (RNNs) are being employed. Several implementations of drug discovery have currently been analysed and supported the power of the technology in quantitative structure-property relationship (QSPR) or quantitative structure-activity relationship (QSAR). In addition, de novo design promotes the invention of significantly newer drug molecules with regard to desired/optimal qualities. In the current review article, the uses of AI in pharmacy, especially in drug discovery, drug delivery formulation development, polypharmacology and hospital pharmacy are discussed.*

Keywords: Artificial intelligence, Artificial neural network, Drug discovery, Drug delivery research, research, Hospital pharmacy

I. INTRODUCTION

Artificial Intelligence (AI) is a stream of science related to intelligent machine learning, mainly intelligent computer programs, which provides results in the similar way to human attention process.¹ This process generally comprises obtaining data, developing efficient systems for the uses of obtained data, illustrating definite or approximate conclusions and self corrections/adjustments.² In general, AI is used for analyzing the machine learning to imitate the cognitive tasks of individuals.^{2,3} AI technology is exercised to perform more accurate analyses as well as to attain useful interpretation.³ In this perspective, various useful statistical models as well as computational intelligence are combined in the AI technology.⁴ The progress and innovation of AI applications are often associated to the fear of unemployment threat. However, almost all advancements in the applications of AI technology are being celebrated on account of the confidence, which enormously contributes its efficacy to the industry. Recently, AI technology becomes a very fundamental part of industry for the useful applications in many technical and research fields.^{3,4} The emergent initiative of accepting the applications of AI technology in pharmacy including drug discovery, drug delivery formulation development and other healthcare applications have already been shifted from hype to hope.^{5,6} The uses of AI models also make possible to predict the in vivo responses, pharmacokinetic parameters of the therapeutics, suitable dosing, etc.^{2,7} According to the importance of pharmacokinetic prediction of drugs, the uses of in silico models facilitate their effectiveness and inexpensiveness in the drug research.⁸ There are two key classes of AI technology developments.⁹ The first one comprises the conventional computing methodologies including expert systems, which are capable of simulating the human experiences and illustrating the conclusions from the principles, like expert systems.¹⁰ The second one comprises the systems, which can model the mode of brain functioning employing the artificial neural networks (ANNs).⁹ In specific, various ANNs like deep neural networks (DNNs) or recurrent neural networks (RNNs) control the evolutions of AI technology. In Merck Kaggle¹¹ and NIH Tox21 challenge,¹² DNN issues show the greater predictivity than the baseline machine learning methodologies.^{3,14} The machine learning employs suitable statistical methodologies with the



capability to learn with or devoid of being unequivocally programmed.¹³ In addition, de novo design promotes the invention of newer drug molecules with regard to optimal or desired qualities.¹⁴ In the current review article, the uses of AI in pharmacy, especially in drug discovery, drug delivery formulation development, polypharmacology and hospital pharmacy are discussed.

MILESTONES IN AI:

The first use of the phrase- ‘Artificial Intelligence’ was appeared in 1956. However, the concept of AI was employed since 1950 with the uses of problem-solving as well as symbolic methodologies.⁵ Important milestones in the area of the AI uses are presented in Table 1.



Fig.1 Important milestones in the area of AI

CURRENT PHARMACEUTICAL CHALLENGES AND THE ROLE OF AI

In the pharmaceutical industry, research on small molecules for better products and customer satisfaction is ongoing due to their multiple advantages. The chemical synthesis process is simple, while the synthetic derivative preparation is economical. Thus, many stable and potent small-molecule-loaded formulations are present in the pharmacy sector. Except for the treatment of rare diseases, many innovative small molecules face competition from generic molecules, and complex data are required for them to be launched, along with clinical trials. These processes increase the economic pressure on companies to engage in more innovation. However, the biomolecular drug industry is still growing at a rapid



pace to compensate for the crisis induced by the small molecular size and poor dissemination of research and innovations. Small-molecule actions are based on their conformation and reactivity. Biomolecules, which are large units, mostly contain amino acids from the protein source along with nucleotides or ribonucleotides for the nucleic acid. Their stability and function are also influenced by the supramolecular sequence and the spatial conformation. Some biomolecules are very successful products, such as insulin and adalimumab. The pharmacokinetic aspects of these molecules are complex, as infusion is the preferred and most usable route of administration for these biomolecules. Pharmacokinetic modulation and molecular stabilization are important aspects of nucleic acid-based research. The pharmacokinetic exposure and enhancement of these molecular forms are crucial goals. New technological advancement may be helpful to address these challenges and solve related issues. Although there is huge scope for AI in drug delivery innovation and drug discovery, it still presents some major limitations that ultimately require human interference or intellectuals to interpret the complex results. The major contributions of AI predictions are based on the datasets, but the interpretation of the results, owing to the gray zone, require human interference to reach the appropriate conclusion.

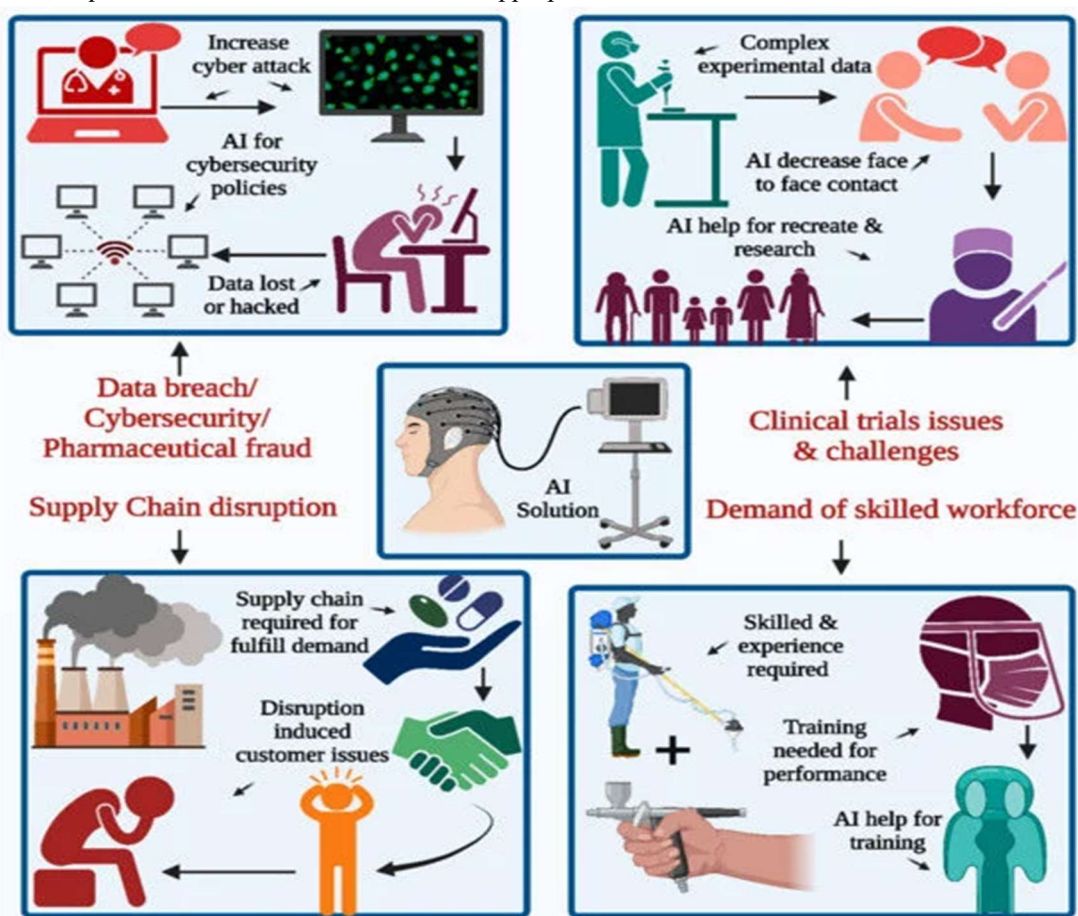


Fig. 2 Different supervised and unsupervised AI learning models/tools for pharmaceutical applications

AI can experience issues with algorithm bias regarding the processing of information for predictions and the assessment of hypotheses. Moreover, it is not uncommon for docking simulations to result in the discovery of inactive molecules. Therefore, a critical analysis of these parameters still requires human involvement for effective decision-making and cross-verifications, to rule out system bias issues. Nevertheless, there is huge potential in AI for possible application, and thus, extensive work may be able to reduce the limitations associated with AI and make it effective and reliable [35]. Regarding AI, the methodology employed involves the utilization of machine learning or its subsets, such as deep learning and natural language processing. The learning process can be either supervised or unsupervised, and the



type of algorithm employed is also a crucial factor. Supervised learning is a machine learning methodology that involves the use of known inputs (features) and outputs (labels or targets), as opposed to unsupervised learning, which deals with unknown outputs. The supervised approach involves the prediction of output, such as labels or targets, based on multiple inputs or features. On the other hand, unsupervised classification aims to create groups that are homogeneous in terms of features [36]. In pharmaceutical product development, various AI models have been explored to enhance different aspects of the process. A list of commonly explored AI models in this domain is described in Figure 2

AI IN HOSPITAL PHARMACY

There are several applications of AI in hospital pharmacy based health care system in organizing dosage forms for individualized patients, selection of the suitable or available administration routes or treatment policies.

Maintaining of medical records: Maintenance of the medical records of patients is complicated task. The collection, storage normalizing, tracing of data are made easy by implementing the AI system. Google Deep Mind health project (developed by Google) assists to excavate the medical records in short span of time. Hence, this project is a useful one for better and faster health care. The Moor fields Eye hospital NHS is assisted by this project for improvement of eye treatment.

Treatment plan designing: the designing of effective treatment plans is possible with the help of AI technology.15 When any critical condition of patient arises and selection of suitable treatment plan becomes difficult, then the AI system is necessary to control the situation. All the previous data and reports, clinical expertise, etc., are considered in the designing of treatment plan as suggested by this technology. A program is launched by IBM Watson to help oncologists.

Assisting in repetitive tasks: AI technology also assists in some repetitive tasks, such as examining the X-ray imaging, radiology, ECHO, ECG, etc., for the detection and identification of the diseases or disorders.15 Medical Sieve (an algorithm launched by the IBM) is “cognitive assistant” having good analytical and reasoning ability. A medical start-up is necessary for the improvement of patient condition by combining deep learning with medical data. A specialized computer program is available for each body part and used in specific of disease conditions. Deep learning can be employed for almost all types imaging analyses, such as X-ray, CT scan, ECHO, ECG, etc.

Health support and medication assistance: Recent years, the uses of AI technology are recognized efficient in health support services and also, for the medication assistances.6 Molly (a start-up designed virtual nurse) receives a pleasant voice along with a cordial face. Its aim of it is for helping patients to guide the treatment of patients as well as supporting them with chronic condition between the doctor’s visits. Ai Cure, is an app existing in Smartphone’s webcam, monitors patients and assists them to control their conditions.

AI helps to people in health care system: It is capable of collecting and comparing the data from social awareness algorithms.6 The vast information recorded in healthcare system involves the medical history of the patients along with the treatment history profile from the birth, habits as well as life-styles of the patients.

AI APPROACHES FOR DRUG DISCOVERY

The drug discovery procedure begins from the available results attained from different resources like high throughput screening modelling, fragment screening modelling, computational modelling and existing data reported.1,24 A schematic outline of the drug discovery procedure is shown in Figure 3. In drug discovery procedure, the structural characterization of drug molecules can directly or indirectly be analyzed by computer-assisted design approaches and after this, organic synthesis of drug molecules is done. The synthesized drug molecules or collected drug compounds are subjected to high throughput screening in primary assay and then, these are counter screened and evaluated for their bioavailability in secondary assays along with successful structure activity relationship (SAR) analysis. The drug discovery interchanges amongst induction and deduction processes. Thus, the interchangeable cycle of inductive–deductive process ultimately guides to attain the optimized lead molecules.1 The automation of specific portions of the inductive–deductive cycle decreases the unpredictability and inaccuracy; thus, improves the effectiveness of drug discovery procedure. Chemical and pharmaceutical manufacturers examine and derive numerous patents as well as



genomic data-based scientific science information by applying the deep learning software, e.g., “NVIDIA DGX-1”. Human beings cannot operate total available information for the advancement of scientific research. AI supercomputers are able to receive and examine the information for identification the association in-between the compounds to offer newer drug molecules.

The applications of AI in drug discovery process concerns the use of chemical space.^{1,42} In fact, the chemical space offers the phase for the identification of new molecules since it is achievable to computationally itemise the desired molecules.⁴³ In addition, the machine learning and related predictive tools also help for the identifications of target-specific effective molecules.⁴⁴ The process of selecting a successful new drug molecule from large quantity of pharmacological active chemical entities is the toughest part of the whole phenomenon.⁴⁵ Benevolent AI is utilized for the purpose of processing fewer molecules with much more surety about their activity. In this regard, de novo design necessitate the understanding of organic chemistry for the synthesis of in silico molecules and the virtual screening modelling that perform as the replacements for many biochemical as well as biological testing to measure the efficiency as well as toxicity profiles.⁴⁶⁻⁴⁹ The aim of de novo design in the drug discovery is the invention of newer active molecules without the uses of reference molecules.⁴⁷ Finally, the active learning algorithms permit the discovery of new molecules with the potential actions against the target-setting of diseases or disorders. Several in silico methods for the selection of profiles like ligand-based design approaches or molecular structure-based design approaches may be employed along with the accessible information on the small molecule modulator probes or the features of structural biology.⁵⁰ In silico molecules is obtaining the next generation AI. There are various proposals and software solutions accessible for it. This design is not useful in drug discovery; but, it is connected to the generation of components possessing difficulty in synthesis.

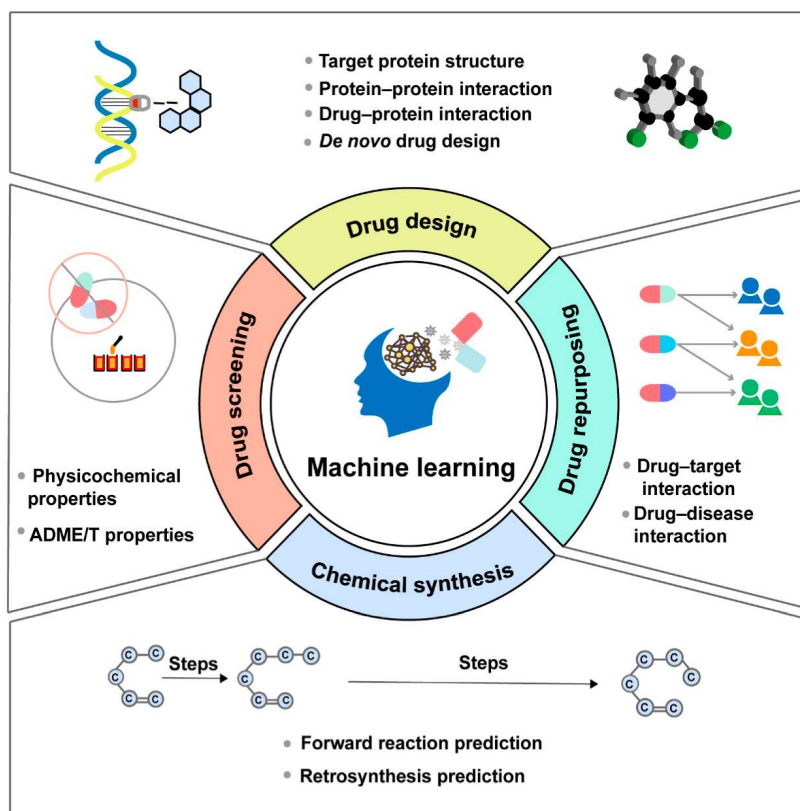


Fig.3 Machiene learning empowering drug discovery

Although recursive neural networks are applied for de novo design, it is mainly introduced in the field of natural language processing.⁵¹ The sequential information is taken as input by recursive neural networks. As the molecular structures are



encoded as a series of letters by SMILES strings, recursive neural networks are employed for generating the chemical structures of molecules. The neural networks are taught the grammar of SMILES strings by mean of training recursive neural networks with a wider setting of chemical compounds from the existing/available chemical compounds from existing compound collections (e.g., ChEMBL). The recursive neural networks have the capability for the processing of a high fraction of authentic SMILES strings.⁴⁹ This approach is also applied for the creation of newer peptide structures.⁵¹ The reinforcement learning is also used in favour of the generated chemical molecule towards the desired characteristics.⁵² Another useful strategy is transfer learning used for generation of newer chemical structures processing a proper biological characteristics. This strategy possesses two steps. The step1 consists of training of the network for learning SMILES grammar. The step 2 consists of continued training with compounds possessing proper desired property. Such few extra epochs of training are enough in favour of the generation of newer compounds as into a chemical space possessed by the active molecules. Depending upon these approaches, in a work, synthesis of five molecules is done with the conformation of the design activity for four molecules against the nuclear hormone receptors.

AI APPROACHES FOR DEVELOPMENT OF DRUG DELIVERY SYSTEMS Generally, the designing of drug delivery systems is related to some disadvantages like prediction of the relationship amongst the formulation factors and responses.^{2,55} This is also related to the therapeutic outcomes and the unpredicted occurrences. In the designing of different kinds of intelligent drug releasing systems, the on-demand dose adjustment or the rates of drug releasing, targeted releasing and drug stability are the important factors.⁵⁶ Concerning the self-monitoring systems for releasing of drugs, the suitable algorithms are useful for controlling the quantity as well as the period of drug releasing.² Therefore, AI approaches are useful for the prediction of the drug dosing efficacy and drug delivery potential of the drug delivery dosage forms. Solid dispersions: The ANN modeling combined with experimental design has been employed to develop solid dispersions of carbamazepine using poloxamer 188 and Soluplus®.⁵⁷ The aim of the preparation of carbamazepine solid dispersions was to improve the carbamazepine solubility and dissolution rate. These carbamazepine-Soluplus®-poloxamer 188 solid dispersions were synthesized via the solvent casting technique. In a research, a modeling of ANN (a feed-forward back propagation) with the logistic sigmoid activation function has already been employed for the analyses of linking amongst different variables as well as dissolution properties for the optimization of dissolution rate of drug.⁵⁸ In this work, to prepare the solid dispersions of drug, poly (vinyl pyrrolidone)/polyethylene glycol mixtures were used as carriers. The applied ANNs assisted modeling established an appropriate prediction for the solid dispersion preparations of drugs with desired dissolution properties with along-standing physical stability.⁵⁸ Emulsions and microemulsions: ANNs have also been utilized for the formulation development of stable emulsions (oil/water).⁵⁹ The optimization of the fatty alcohol concentration to formulate emulsions (oil/water) was analyzed in this work. The independable variables (factors) analyzed in this work were concentrations of lauryl alcohol and time. The dependable variables (responses) were droplet size, zeta potential, viscosity of the model.

Table 1. Popular AI model tools used for drug discovery

<i>AI Model Tools</i>	<i>Summary</i>
<i>Deep Chem</i>	An open-source library that provides a wide range of tools and models for DeepChem drug discovery, including deep learning models for molecular property prediction, virtual screening, and generative chemistry.
<i>RDKit</i>	A widely used open-source cheminformatics library that offers various functionalities for molecule handling, substructure searching, and descriptor calculation. It can be integrated with machine learning frameworks for drug discovery applications.
<i>ChemBERTa</i>	A language model specifically designed for drug discovery tasks. It is based on the Transformer architecture and is pretrained on a large corpus of the chemical and biomedical literature, allowing it to generate molecular structures, predict properties, and assist in lead optimization.



<i>GraphConv</i>	A deep learning model architecture that operates on molecular graphs. It has been successful in predicting molecular properties, such as bioactivity and toxicity, by leveraging the structural information encoded in the graph representation of molecules.
<i>AutoDock Vina</i>	A popular docking software that uses machine learning techniques to predict the binding affinity between small molecules and protein targets. It can be used for de novo drug design and lead optimization.

AI TOOLS APPLICATION IN DOSAGE FORM DESIGNS

The human body system is divided into several compartments to understand the impact of drug delivery. The compartments are further simplified based on biological membranes. Physicochemical barriers are vital for biological compartments and can be implemented based on the mode of drug delivery inside the body. One of the most significant criteria for efficient drug delivery system monitoring is the rate of permeation based on the route of administration. The orally administered drug, after entering the gastric environment, must permeate through the intestinal or gastric epithelium. This step is vital for the further distribution of the drug into the bloodstream. The distribution step conveys the drug to the target site, which can be tissue or any of the specific cellular components. Intracellular molecules can also act as targets for drug entry into the body. Most of the permeation of drugs is facilitated through biological barriers, either passively or actively. Passive diffusion is based on the drug's molecular features. The in silico models are used to predict drug distribution through computation analysis, but these results are somewhat different from the actual drug distribution study. The drug's interaction with biological components and the availability of the drug in biological environments have a great impact on the drug's fate in the body. This process is governed by the molecular features of the drug. For many biologically active entities and small molecules, passive permeation is inefficient and requires a specific drug delivery system. The active permeation process is driven by membrane transport and depends on complex biological interactions. This complex process must be explored by using many specific parameters through computation and systematic modeling approaches. This newer computational model is used to study the pharmacokinetic parameters of the drug delivery system. One of the major loopholes present in the research and development of the pharmacy industry is the predictability of preclinical models. The predictability assumption is based on the selected parameters, and the same applies to complex in silico models as well. All these cases are linked to drug interactions with membranes and can be better analyzed by the modeled environment, is presented. This modeled environment can be studied and analyzed more effectively through AI [81–83]. AI provides sophisticated technology for the analysis of such multilayer data. The thoroughness of the analysis will contribute to a better understanding of the research units. The systematically applied model along with parameter evaluation is based on many factors, such as simulation, scoring, and refinement, in each step of the research to determine the best outcomes. AI could provide an automated system that can be implemented for all these functions for better guessing and predicted refinement of the data for consistent improvement. For better AI training in the biological environment, a proper understanding of the drug–biological interaction is essential, which is indicated by the system biology type of the databases. Pharmacokinetic studies can be performed using many novel AI technologies, such as artificial neural networks. Along with this, many databases are provided by AI, such as chemical, genomic, and phenotypical databases, for a better understanding of the drug interaction and the effective study of the molecules' complex unit roles within the same. Some of the methods are also applied to study the impact of the drug delivery system on the pharmacokinetics of the drug, for an effective understanding of the disposition and toxicity. Many new approaches to drug delivery systems involve the design of quality attributes along with critical attributes and studying their impacts on experimental trials before actual experiments.



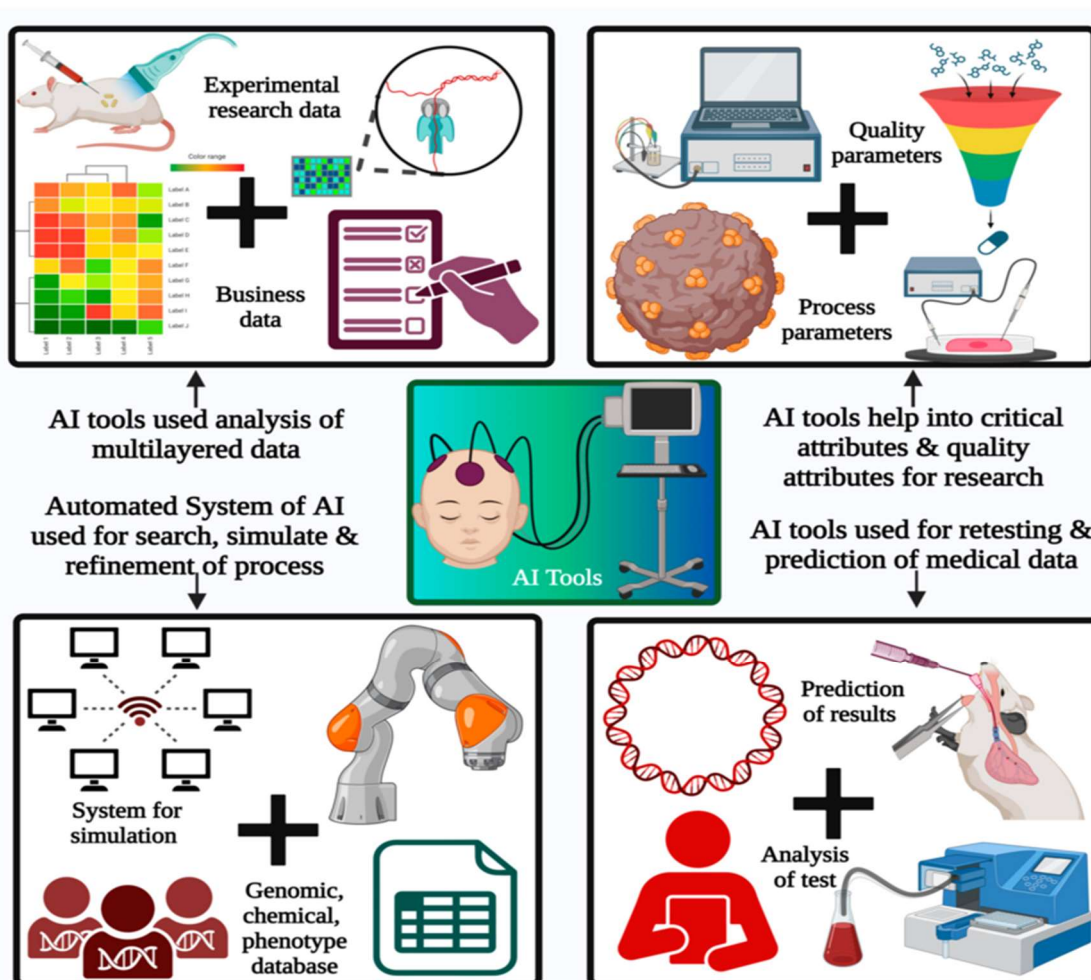


Fig. 4 Application of AI tools in the pharma sector

The benefits of AI are that it collects information from multiple sources and provides indications for the selected drug delivery system to work as per the anticipated results. The evaluation of the molecular information, patient data, and pharmacokinetic data are considered part of the complex data for analysis for the possible selection of the best active pharmaceutical against patient diseases or requirements. The passive type of AI is implemented for the identification of molecular entity features against those of known molecules for comparison. Effective treatment depends on the accuracy of the selection of drug delivery systems, which are provided by AI. AI is also useful for the drug discovery process along with the drug repurposing method. This addresses the application of the existing therapeutics to that of the new disease. The requirement of the patients and disease condition are major factors contributing to formulation, pharmacokinetics, and drug development. One of the major challenges associated with the application of AI in full scope to develop delivery systems is the availability of databases with detailed information. This is required for the evaluation of the models, along with parameters, in an unbiased way. AI provides help for future applications by using current knowledge. A large quantity of the data can be handled or digested by using AI tools for a better approach to the rational design of the product, as presented in Figure 4. A more vigorous codification inside the knowledge database can be performed with excellent self-supervised experimental results and related to proper parameter recording.

Application of AI tools in the pharma sector. AI tools are helpful for the analysis of multilayered data. Automated AI systems are used to perform effective searches, simulations, and refinements of data and processes involved in research and product development. The system biology database, chemical database, genomic database, phenotypic database, and



AI bots are used for better exploration of drug models, drug release, and activity predictions along with recommendations for effective drug delivery systems.

II. CONCLUSIONS

AI is transforming drug delivery technologies, enabling targeted, personalized, and adaptive therapies. By leveraging AI's capabilities in data analysis, pattern recognition, and optimization, pharmaceutical researchers and healthcare professionals can enhance drug efficacy, minimize side effects, and improve patient outcomes. AI-based methods have revolutionized the field of pharmacokinetics and pharmacodynamics. They offer several advantages over traditional experimental methods. AI-based models can predict pharmacokinetic parameters, simulate drug distribution and clearance in the body, and optimize drug dosage and administration routes. AI-based computational methods for PBPK models can simplify the development of such models and optimize their parameters, reducing the need for animal studies and human clinical trials. Computational pharmacetics, facilitated by AI and big data, revolutionizes the drug delivery process by providing a more efficient, cost-effective, and data-driven approach. It enables the optimization of drug formulations, personalized therapies, regulatory compliance, and risk reduction, ultimately leading to improved drug manufacturing processes and enhanced patient outcomes. Overall, the integration of AI technologies holds great promise for accelerating drug development, improving patient outcomes, and revolutionizing the pharmaceutical industry, promoting its evolution from era 4.0 to era 5.0.

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