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REVIEW

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Influence of artificial intelligence in modern pharmaceutical formulation and drug development

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Abstract

Background Artificial intelligence (AI) revolutionized the formulation and development of modern pharmaceuticals. With the help of AI, researchers can now optimize drug design, develop formulations, and streamline clinical trials in a much accurate and efficient way. Drug development might be greatly expedited and time-consuming procedure; however, with the help of AI this are significantly reduced.

Main body of abstract The main advantages of AI in pharmaceutical formulation are its capacity to analyse vast amounts of data and spot patterns and connections that human researchers would miss. Various tools and technologies, such as ANN, fuzzy logic, neuro-fuzzy logic, and genetic algorithm are used for analysing the date, of which ANN is popular and mostly used. AI enables the discovery of novel pharmacological targets and the creation of more potent medications. AI may also be used to improve medication formulations by forecasting the solubility, stability, and bioavailability of drug candidates, increasing the likelihood that clinical trials will be successful.

AI is also applied in designing clinical trials, reducing the time and cost of the process by identifying patient populations that are most likely to benefit from the treatment. Additionally, AI can monitor patients during clinical trials, detecting real-time adverse effects and adjusting dosages to improve patient outcomes.

Conclusion AI is a potent pharmaceutical formulation and development tool, allowing researchers to analyse vast amounts of data, optimize drug formulations, and streamline clinical trials. As technology develops, experts anticipate that AI will increasingly show a crucial part in drug development, enabling faster, more efficient, and more effective treatments for various diseases.

Keywords Artificial intelligence, Machine learning, Nano medicine, Nano robots, Pharmaceutical formulation, Drug development

Background

The phrase "Artificial Intelligence" (AI) is a general term that describes the least amount of human intervention possible when utilizing a computer to imitate intelligent behaviour. AI is the subfield of computer science that deals with programming to solve issues [1]. It has developed into a discipline that addresses problems in business, engineering, and healthcare. The creation of expert systems is one use for AI. An inference engine, an information base, and a user interface make up an expert system. AI possesses distinctive characteristics that enable it to reason and execute actions with the highest probability of accomplishing a specific objective. AI accomplishes this through a combination of algorithms that simulate even the most fundamental human intellectual capabilities. Nowadays, AI is gaining momentum

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across multiple sectors, and the pharmaceutical industry is at the forefront of this trend. In the past, formulators have favoured statistical methods, for example response surface approach, for analysing design space. However, optimization using this approach has the potential to be deceptive, especially when dealing with a complex formulation. Two methods that can tackle the issue at hand have been developed as a result of recent developments in mathematics and computer science. The first technique involves using neural networks to replicate how the human brain processes information. The second technique is genetic algorithms, which mimic biological systems' self-organizing and adaptive natures through an evolutionary method. The practical requests of AI in the pharmaceutical production house are highlighted in this paper, including drug research and development (R&D), drug repurposing, increasing pharmaceutical output, clinical testing, etc. These applications reduce the need for human labour and accelerate the drug development process [2]. Over the past few years, the pharmaceutical manufacturing company has significantly improved its data digitalization. To answer challenging clinical problems, acquiring, examining, and applying this knowledge is difficult due to this digitization. AI is used to address this since it can manage enormous volumes of data with increased automation. However, it does not endanger the physical existence of humans. AI uses hardware and software to analyse input data and learn from it in order to accomplish specified goals. This review explains that its services in the pharmaceutical sector are constantly growing. The rapid advancement of AI-guided automation, according to the McKinsey Global Institute, will fundamentally alter how society views labour. Every stage of the pharmaceutical product life cycle, including drug discovery, optimization, formulation development, characterization, quality testing, marketing, and post-marketing surveillance, can integrate AI to improve its efficacy [3].

Tools, technology, and networks

Artificial neural networks (ANN)

Machine learning (ML) is an essential subdivision of AI. A big part of ML is deep learning, which involves ANN. The ANN is made up of multilayer functional units that mimic how electrical impulses are transmitted in the human brain, i.e. it mimics a human brain. They are mainly biologically motivated systems. It takes input and learns directly from input data; primarily, neurons work mainly on the summation of all information and express an output [4].

The fundamental component of biological neural systems is the neuron. Neurons are electrochemical cells; they receive signals from one neuron and transmit signals to other neurons [4]. Like humans, the ANN system has a primary component known as a "perceptron" or node. Nodes are arranged into layers, and artificial neurons analyse input to create an output that is sent to the following perceptron. It is categorized into two states, supervised learning (SL) and unsupervised learning. In unsupervised learning, the network receives input data and identifies patterns or structures within the data thereby condensing the data into a more compact form [5].

In SL, the network is "taught" by receiving guidance during the learning process. In this SL, the network is given the relevant input and output data. The connection between the input and output data is established via the network. SL is considered the most popular and valuable network for formulation purposes [4, 5].

The arrangement of interconnected neurons in a neural network is called network architecture. There are various types of network architecture; among them, a multilayer perceptron (MLP) network is one of the best suitable examples.

X1, X2 & X3 are input variables, and Y is the output. The number of input, output, and hidden layers depends on the condition and the researcher's plan depicted in Fig. 1 [6].

Fuzzy logic

Another tool of AI is fuzzy logic. People extensively use fuzzy logic in problem-solving. When ANN accompanies it, it cooperates to understand the formulation and optimization process [4]. Conventional sense relies on either 'true' or 'false.' So, this hypothesis falls between either in actual or wholly false part. Since the premise is true, the membership function in the true set is 1; otherwise, it is 0 in the false set [4].

Neuro-fuzzy logic

The main motto of fuzzy logic is to give in simple forms. Neural network modelling is necessary to form it. Neuro-fuzzy logic, by its name, is understood that neuro-fuzzy logic is composed of neural networks and fuzzy logic. It

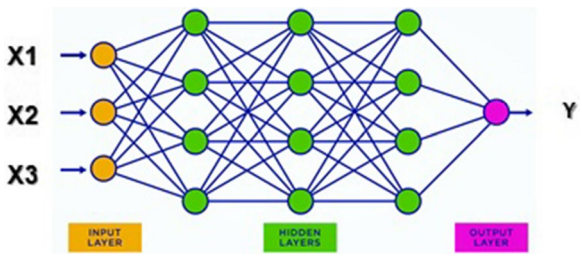

Fig. 1 Schematic diagram of artificial neural network

combines ANN's learning capacity with generality and fuzzy logic's ability to explore complex concepts. Neuro-fuzzy logic is tightly well suited to process data mining. It can develop good models from data and express the linguistic IF_THEN rules [4, 5].

Genetic algorithm

John Holland introduced genetic algorithms (GA) in the 1970s [5]. Like ANN, GA is also a biologically motivated system. Natural selection, the primary tenet of its genetic variation, imitates the fundamental principles of evolution over a generation. We create a genetic algorithm to select the best and most effective solution. They provide a 'search' strategy that is excellent for optimisation. An iterative procedure would be used to advance the trial population. As part of this procedure, we form a starting population and evaluate each member's fitness [4]. The fittest solutions change into 'parents' of the subsequent generations. It becomes a more ideal answer by including some introduction of recombination and mutation, which produces a larger degree of new stuff in the population. The genetic algorithm needs a criterion of "fitness." It is variable from problem to problem [5].

The best solution is found by creating a number of potential solutions when an ANN and a genetic algorithm are combined. These candidates are selected based on their fitness according to predefined criteria. Generating a new population of solutions is accomplished by utilizing the most effective solution and incorporating crossover and mutation techniques. The process persists until it fulfils the desired requirements, at which juncture the repetition is terminated [4].

An optimization technique is needed to develop a pharmaceutical product to find the best combination of ingredients and techniques. Researchers have proven that the combination of ANN and GA possesses the requisite solutions for developing dosage forms.

Evolutionary computing

It is just a definition of a computational technique that uses heredity, recombination, mutation, and selection to solve a problem. One particular branch of evolutionary algorithms has been used in formulation research [5].

Life cycle of pharmaceutical products

AI can support decision-making, enable rational drug design, determine the best course of a patient's treatment with personalized medications, accomplish the clinical data produced, and utilised that data to create new drugs in the future [7]. From the lab to the bedside, it is logical to assume that AI will contribute to creating pharmaceutical products. Eularis created the E-VAI analytical and decision-making AI platform, which employs ML algorithms and a user-friendly interface to create analytical roadmaps based on rivals, crucial stakeholders, and the market share currently held to forecast critical factors in pharmaceutical sales [8]. This boosts sluggish sales and gives marketing directors the ability to foresee where to make expenditures. It also helps them allocate resources for optimum market share growth. Figure 2 presents an overview of several AI uses in drug discovery and development.

AI in drug discovery

The research and development of new drugs is a challenging, expensive, and lengthy task. On average, the R&D cycle spans around 10–15 years. Despite the significant financial investment made by the pharmaceutical industry, pursuing the next blockbuster drug persists. This R&D is since only one in every ten potential drug candidates completes phase I clinical trials and attains regulatory approval [9, 10]. The cost and time constraints associated with developing newer therapeutic compounds may be a contributing factor in the pharmaceutical industry's acceptance of AI [11].

The tools and technologies employed by AI are valuable in rapidly identifying hit and lead materials, validating drug targets, and optimizing drug structure design, potentially benefiting the healthcare industry by reducing the cost and timeline associated with discovering novel molecules. However, despite these advantages, AI must still overcome significant data hurdles, including the data's complexity, growth, diversity, and ambiguity [12, 13].

The chemical structure that would elicit the desired reaction at the target location may be predicted using a variety of in silico approaches. This structure can then be improved to meet a variety of criteria, such as potency, safety, solubility, permeability, and synthetic tractability. These methods also make it possible to plan the production of the compound and anticipate the molecule's physicochemical characteristics [13, 14].

By utilizing both structure- and ligand-based methods, along with all available data, it is feasible to hasten the elimination of non-lead compounds. Recently, researchers have employed the quantitative structure–activity relationship (QSAR) modelling device for screening potential pharmacologically active compounds from a pool of one million candidates. Moreover, the deep learning approach, an evolution of the earlier ML approach, can now handle the massive amount of data gathered throughout the drug discovery and development procedure [15, 16].

Using a computer model based on the QSAR, large quantities of compounds or certain physicochemical qualities, such as log P or log D, may be swiftly

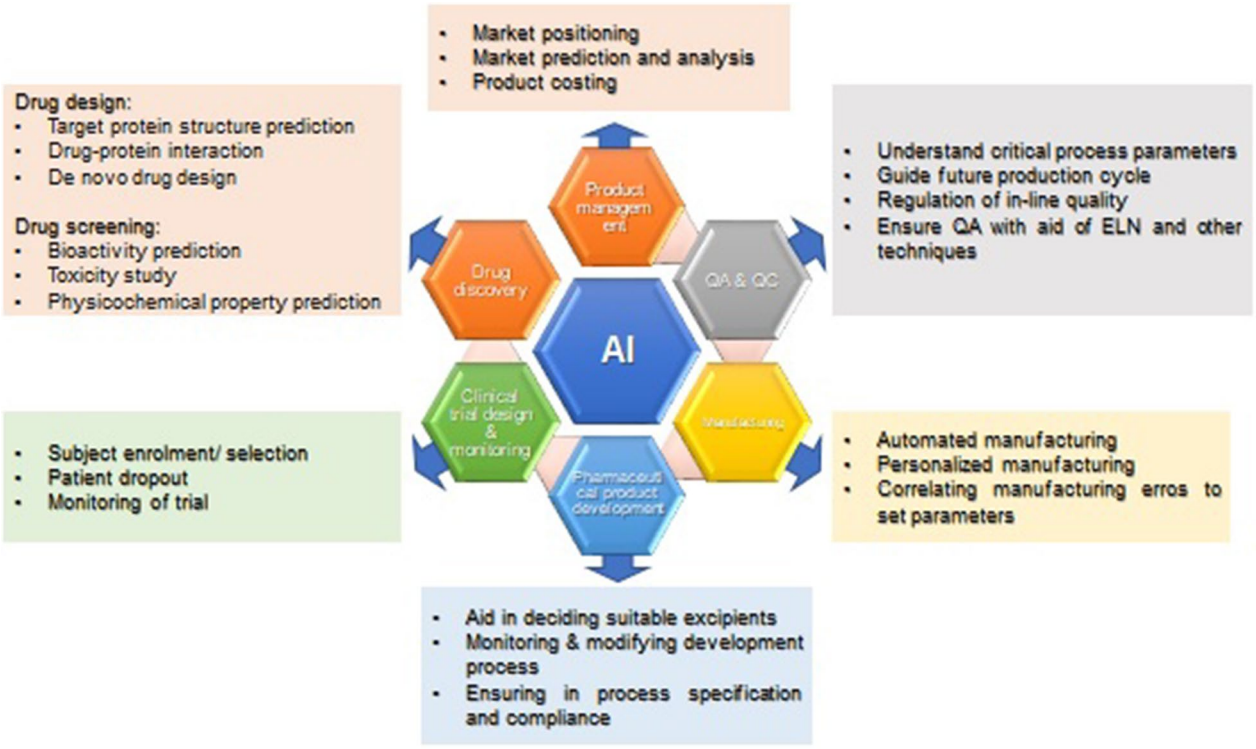

Fig. 2 Applications of AI in various pharmaceutical business subfields, including pharmaceutical product management and drug development

predicted. These models, however, are far from being able to forecast with any degree of accuracy complex biological traits like a compound's efficacy and undesirable side effects. Additionally, QSAR-based models have issues with limited exercise groups, erroneous investigational facts, and a need for more trial validations. To address these problems, researchers can employ newly developed AI methodologies, such as Deep Learning (DL) and pertinent modelling lessons, to assess the safety and effectiveness of pharmaceutical molecules through extensive data showing and study [17, 18].

DL models beat traditional ML techniques in 15 drugs candidate-related absorption, distribution, metabolism, excretion, and toxicity (ADMET) data sets regarding predictability. Drug metabolism sites are identified using artificial intelligence (AI) techniques like XenoSite, FAME, and SMARTCyp. By displaying molecule distributions and properties, the huge virtual chemical space suggests the existence of a molecular topographic map. Chemical space visualization's idea is to collect positional information on nearby molecules to hunt for bioactive compounds; thus, virtual screening (VS) helps choose appropriate molecules for future investigation. PubChem, ChemBank, DrugBank, and ChemDB are a few open-access chemical databases.

For the purpose of locating prospective novel drugs, AI-based QSAR approaches, such as decision trees, support vector machines, random forests, and linear discriminant analysis (LDA), have evolved from QSAR modelling tools [15, 19, 20].

We have included a list of a few AI technologies used throughout the drug development phase in Table 1 to help readers understand. Figure 3 summarizes the various AI models used during drug development methods. Physicochemical characteristics, bioactivity, toxicity, target proteins, drug interactions, drug-protein binding interactions, and de novo synthesis of certain organic synthetic compounds are all predicted by these models [21].

AI in drug development

An acceptable dosage form with the essential delivery qualities must then include a unique medicinal component. In this case, AI can take the place of the conventional approach of trial and error [22]. With the use of QSPR, a variety of computational techniques may resolve issues in the formulation design area, such as instability issues, dissolving, porosity, and many more [23]. Decision-support technologies use rule-based algorithms to choose the kind, nature, and amount of the excipients depending on the physicochemical properties of the

Table 1 The AI techniques/tools used in the drug discovery process

Name of tools	Application
Reinforcement learning	Used to optimize drug combinations and dosages by considering multiple interacting variables and maximizing desired outcomes
DeepChem	Open-source library for deep learning in chemistry and drug discovery
DeepTox	Open-source deep learning framework specifically designed for toxicity prediction and assessment
Neural graph fingerprints	Method for encoding molecular structures as fixed-length feature vectors using neural networks, suitable for various applications in drug discovery, such as virtual screening, lead optimization, and property prediction
PotentialNet	Ligand-binding affinity prediction based on a graph convolutional neural network (CNN)
Predictive ADME/Tox modelling	Tools employ ML techniques to model and predict the absorption, distribution, metabolism, excretion, and potential toxicity of drug candidates
Natural language processing (NLP) tools	Assist in extracting and analysing information from scientific literature, patents, and clinical trial data
Cheminformatics tools	Tools enable the analysis and manipulation of chemical structures and properties
QSAR/QSPR modelling	Correlate molecular properties and structures with biological activities or properties, enabling the prediction of compound behaviour
Deep learning (DL)	Applied in tasks like virtual screening, de novo drug design, and predicting drug properties
Machine learning (ML)	Help predict drug-target interactions, analyse biological activity, and optimize lead compounds

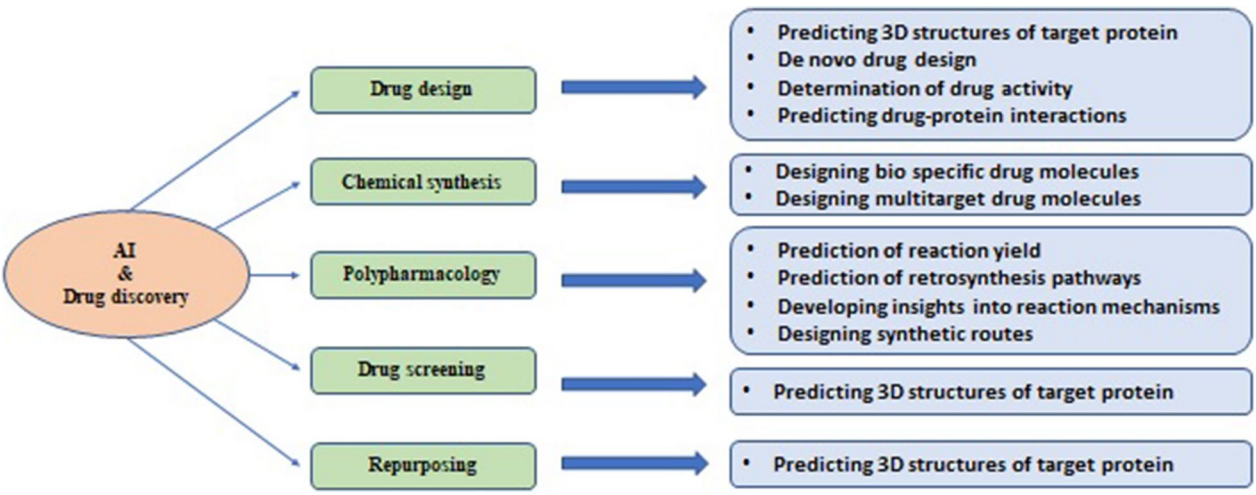

Fig. 3 Different applications of AI in drug discovery

drug. They also use a feedback loop to keep an eye on and occasionally tweak the entire process [24].

Piroxicam direct-filling hard gelatin capsules were designed using a hybrid method that combines expert systems (ES) and ANN in order to achieve the necessary dissolving profile. Based on the input parameters, the Model Expert System (MES) delivers judgements and recommendations for formulation development. Contrarily, ANN make use of backpropagation learning to link the formulation parameters to the desired outcome, enabling trouble-free formulation creation. The control module collaboratively manages this process [22].

Using a variety of mathematical methods, including computational fluid dynamics (CFD), discrete element modelling (DEM), and the finite element method (FEM), researchers have investigated the effects of the powder's flow property on the die-filling and tablet compression processes [25, 26]. CFD may also be used to examine how tablet shape affects the profile of the tablet's disintegration [27]. Integrating these mathematical models with AI may have a huge positive impact on the rapid manufacturing of pharmaceutical products. Technologies incorporating AI have evolved into versatile tools that find wide application in various stages of drug development. These stages include identifying and validating drug targets, designing new drugs, repurposing existing drugs, enhancing R&D efficiency, aggregating and analysing biomedicine data, and making informed decisions regarding

patient enrolment in clinical trials [17, 28, 29]. These prospective applications of AI offer the chance to mitigate bias and human interference while addressing the inefficiencies and uncertainties resulting from traditional drug development approaches [30].

Drug repurposing [31], pharmacological features [32], protein characteristics and efficacy [33], drug combination, drug-target interaction [34], and prediction of potential synthetic methods for drug-like molecules [35] are other uses of AI in the pharmaceutical industry. In addition, the identification of associations between drugs and illnesses and the development of novel biomarkers and therapeutic targets allow for the identification of new pathways and targets utilizing omics analysis [36, 37].

AI in drug formulation

Pharmaceutical sciences have seen various formulations, for example solid dispersions, extrudates, pellets, nanoparticles, and liposomes, arise in addition to standard dosage forms. The name "formulation techniques" is given to these techniques because they empower the development of formulations or incorporate functionality into common dosage forms such as tablets. AI applications in formulation techniques are even more worthwhile to investigate in order to create next-generation drug products with desired efficacy and health outcomes because these methods can successfully address a variety of API issues, such as low solubility, stability, bioavailability, and production capability [6].

Controlled-release tablet formulation

Researchers utilize pharmacokinetic simulations and ANN to develop controlled-release formulations [5]. The ANN model learns sophisticated and specialized abilities from the input and output data units with the use of Chem software. In order to anticipate the best tablet formulations based on two ideal *in vitro* dissolution-time profiles and two desirable *in vivo* release profiles, researchers use a sophisticated ANN model. Dissolution is the rate-limiting step in the *in vivo* absorption of the drug since it is linearly proportional to the amount of the drug taken *in vivo*. *In vitro* release patterns are often detected using the difference factors (f_1), and similarity factor (f_2) [38].

Immediate-release tablets formulation

To boost tablet strength, Turkoglu developed a direct compression tablet formulation utilizing hydrochlorothiazide [39]. In a different study, Kesavan and Peck developed a model of a caffeine tablet formulation to describe the diluting agent and binder content in each formulation, processing variables (type of granulator, method of adding binder), and granule and tablet properties (disintegration time, hardness, and friability). These two analyses demonstrated that neural networks performed better than traditional statistical methods. Kesavan and Peck's findings have so been re-evaluated by academics employing a variety of genetic algorithms and neural networks [40]. This presentation illustrated how the relative relevance of the output attributes and the restrictions placed on the several tiers of components and processing factors determined the ideal formulation [41]. Researchers used neuro-fuzzy computing to analyse the same data and frequently created helpful rules that highlighted the most important aspects of any item [5].

Hard gelatin capsule shell formulation

Developing hard gelatin capsule formulations involves using executive tools like ANN and expert systems (ES). ANN stimulate human mental processes, such as generalization, learning, prediction, and abstraction from domain knowledge. With ANNs, the data and statistics collected during investigative work may be transformed into knowledge very quickly, enabling the manufacturer to generate few domain-specific strategies for forthcoming occurrences or forecast the theoretical preparation's characteristics [22]. By extending the Expert Network and conducting analysis, Wendy I. Wilson in 2005, created a capsule shell manufacturing of Biopharmaceutical Classification System II drugs, such as carbamazepine, ketoprofen, naproxen, and ibuprofen. Capsugel's expert system, for the formulation of powders in hard gelatin capsules, was used all over the world despite the drawback of just providing a proposed composition. During the initial test, researchers discovered that the system exhibited low prediction accuracy and a significant error rate. Researchers retrained the ANN using a new dataset, resulting in models with an R2 of less than 70%. Lastly, for the model drugs, the smart hybrid system predicted the quantity of drug soluble around 5%. By using only 10% of the newly generated data for cross-validation, the researchers showed that the system was capable of creating a formulation that satisfied its performance requirements. Researchers presented the system's ability to analyse several BCS class II drugs by considering wettability and intrinsic dissolving properties [42].

Solid dispersions (SD)

One or more APIs dispersed in a solid matrix describe solid dispersions [43, 44]. They are currently a practical and affordable approach for enhancing solubility and bioavailability [45]. They have been extensively employed in academics and industry to overcome concerns with API poor solubility. Many AI-based SD studies have used ANNs to optimize the formulations [46–48]. Researchers utilized ANNs to enhance the floating and drug release

characteristics of SD of Nimodipine prepared with PEG and effervescent mixtures [46]. ANNs were employed to elucidate the relationship between variables such as API concentration, the molar mass of PEG, and temperature in a SD formulated with PVP [49]. Researchers recently developed a model using ML approaches to expect the stability of SD. They employed twenty molecular descriptors to compare eight ML methods. Among these methods, the RF model exhibited the highest estimate precision and provided insights into every input. The top five contributing parameters among the twenty descriptors they picked were the drug loading ratio, relative ambient humidity, storage temperature, preparation temperature, and molecular weight of polymers [50].

Emulsions, microemulsions, and nanoemulsions

Emulsions are biphasic systems with water and oil phases spread over each other and stabilized by an emulsifier [51]. The utilization of micro- and nanoemulsions has the potential to provide a variety of advantages, including increased API bioavailability, superb optical clarity, and improved long-term stability [52–55]. Researchers have published studies on these systems that utilize AI approaches. Kumar et al. regulated the fatty alcohol content with the use of ANNs to produce a steady o/w emulsion. Particle size, zeta potential, conductance, and viscosity were among the emulsion product properties that the ANNs could accurately predict. They also made it possible to quantify the relative significance of the inputs [56]. Gasperlin et al. successfully predicted the structures of microemulsions by creating two ANNs that can determine the kind of microemulsion from the desired composition or a differential scanning calorimetry (DSC) curve, respectively [57]. Additionally, Agatonovic-Kustrin et al. developed a stable microemulsion formulation for the oral administration of rifampicin and isoniazid using ANN model data for treating the ongoing stage of TB [58]. Amani et al. used ANNs to study potential influences on nanoemulsion particle size and discovered that the final particle size's most important factor was the total energy provided during preparation [59]. In addition, Seyed et al. looked into the component concentrations of nanoemulsion to catch the most stabilized structure with minimum cytotoxicity. They found that emulsifier concentration, which was shown to be the primary determinant of nanoemulsion stability, had no effect on cytotoxicity [60].

Self-emulsifying drug delivery systems (SEDDS)

Drugs, oils, surfactants, and occasionally cosolvents are combined in isotropic ways to create SEDDS [61]. SEDDS offer several advantages due to their physical stability, ease of production, and ability to address concerns regarding low drug bioavailability [62]. SEDDS can effectively tackle various API concerns, including enzymatic degradation, gut wall efflux, solubilization, and bioavailability [63]. Fatouros et al. utilized AI techniques such as neuro-fuzzy networks to create a dynamic lipolysis model that simulates medication absorption and predicts the *IVIVC*. Without requiring complex settings, the model showed significant prediction skills, indicating its potential for application in forecasting the *in vivo* behaviour of formulations made of lipids [64]. Utilizing ANNs coupled with I-optimal design, Parikh and Sawant optimized the crucial elements that determine the droplet size of SEDDS. When compared to the quadratic model based on I-optimal design, the ANN-coupled replicas showed the comparative contributions of every factor and were more accurate [65]. Li et al. used multiple linear regression (MLR) and ANN approaches to create quantitative structure-property relationship (QSPR) models that relate the molecular structures of the surfactant, cosurfactant, oil, and drug used in SEDDS with the drug solubility. The researchers found that key factors influencing drug solubility were the ratios of surfactant and oil, as well as the dipole moment and energy of the highest occupied molecular orbital [66].

Other formulation techniques

In addition to these formulation techniques, researchers have applied AI methods to beads and pellets [67–71], microparticles and nanoparticles [72–85], microspheres and nanospheres [86–88], liposomes and nanoliposomes [89], colloidal systems [90], micelles [91, 92], and liquid, solid dosage forms [93].

Scaling up AI across the pharmaceutical value chain

AI and ML are operating revolutions through several manufacturing company. Nevertheless, industries reliant on research, such as pharmaceuticals, are witnessing rapid advancements in these technologies. To speed up the delivery of life-saving medications, AI is re-designing the value chain and extracting insights from diverse data sets to make it highly interoperable [94].

Drug discovery

AI can aid labour and resource-intensive manual drug discovery. Biopharmaceutical companies have the opportunity to employ AI models to identify and validate various methods, leveraging the acquired knowledge to improve their predictive capabilities. AI could have a significant impact on generative modelling for molecule design and protein engineering in the field of molecular design. Although manual data entry remains essential for clinical trials, the utilization of AI-powered data flows allows for the integration of trial data from diverse

sources, enabling the delivery of standardized digital data that seamlessly and automatically transfers to the relevant systems downstream [94].

Manufacturing

AI in biopharma manufacturing might stream crucial data, anticipate process bottlenecks, evaluate current quality control issues, and recommend necessary improvements without the need for time-consuming manual involvement [94].

It could lower operationally expenses and manual oversight in manufacturing operations by permitting tighter control with:

- Quality control
- AI in robotic process automation (RPA)
- AI mock-ups to augment produce & output
- AI-coupled prognostic maintenance to lessen appliance interruption.

Pharmaceutical market of AI

Pharmaceutical companies are turning to AI to reduce financial costs and failure risks. The AI market witnessed growth from US$200 million in 2015 to US$700 million in 2018, and it is expected to reach $5 billion by 2024 [95]. Experts predict that the pharmaceutical and medical industries will experience a 40% growth rate from 2017 to 2024 due to the impact of AI. Numerous pharmaceutical firms have invested in AI and are continuing to do so. They have also worked with AI firms to build crucial healthcare solutions. An example is the partnership between DeepMind Technologies, a Google company, and the Royal Free London NHS Foundation Trust for treating critical renal damage. Figure 4 lists critical pharmaceutical businesses and AI players [12].

Application of AI

Poly-pharmacology

In disease-related molecular networking, poly-pharmacology is the strategic creation of a therapeutic molecule with the innate capacity to interact with numerous targets or pathways (put, "one disease-multiple target"). One can use this method to create a more effective and less hazardous therapy than the currently available one. Several well-known databases that offer details on biochemical pathways, binding strengths, pharmacological goals, and physiological effects are PubChem, CheMBL, Drug Bank, and Binding DB [96, 97]. The AI system can use this data to probe and discover potential poly-pharmacological drugs selectively. One can use the range of available applications, improved computer capacity, and developments in AI technology to change the drug development process.

Quality control and quality assurance

Developing a pharmaceutical formulation within the given timeframe while ensuring quality necessitates a meticulous and scientifically-driven approach to navigate the intricate process successfully. Gathering information involves capturing data about the characteristics of drug compounds and excipients, their interactions, unit operations, and equipment. Various knowledge applications are utilized, such as heuristics, decision trees, correlation, and first-principal models. This information and knowledge inform the decision-making process for production, selection of excipients, and determination of equipment size [98]. Consequently, AI and its networks, technologies, and tools ensure higher product quality, less waste, and increased profit for manufacturing company. Quality-by-Design (QbD) method ensures the improved quality of the generated goods. This approach makes it easy to comprehend the crucial elements in the pharmaceutical production process that might have an impact on the final product's quality.

Product development

The pharmaceutical sector focuses on accelerating pharmaceutical product development, cutting production costs, and enhancing process design for confirming an active medication. Various expert systems can serve as valuable tools for prompt decision-making in the rapid development of pharmaceutical products. An example of a decision-support tool is the rule-based expert system, which represents domain knowledge as a collection of rules structured as IF-THEN statements. These rules utilize input data to assist in addressing specific problems. Each rule consists of two components: the IF part, which establishes an assumption (such as medication insolubility), and the THEN part, which defines the corresponding action to be taken (such as using a soluble filler to address the solubility issue). This type of system, known as a production system or an expert system, represents the fundamental form of artificial intelligence. It functions based on pre-established rules that are provided as knowledge inputs to guide its operations. The choice of excipients for preparing tablets and capsules can be made using these expert systems. Such a system's regulations detail the system's mechanical, chemical, and physical characteristics and the requirements for the finished item. The system's inference engine uses this information to forecast the kind and number of excipients needed to achieve the requirements. This formula is used to create the product, which is then examined to see if it complies with the necessary standards. This information is then

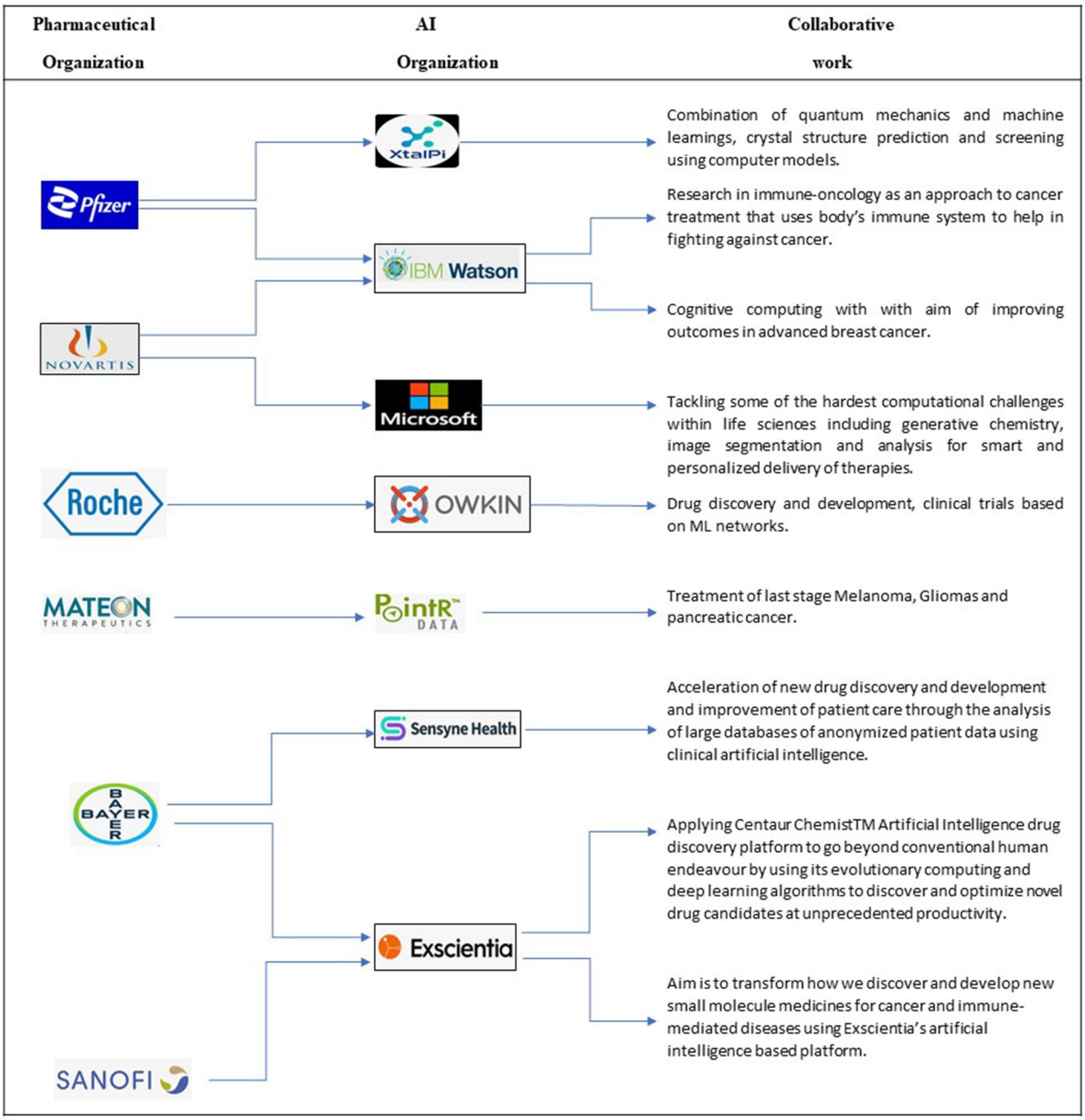

Fig. 4 Leading pharmaceutical firms and their connections to AI companies working in oncology, cardiovascular illness, and CNS disorders. [Pharmaceutical firm's brand name and logo are subject to individual copyright]

fed into the system, which aids with formula optimization (Fig. 5) [24].

The creation of Logica's product formulation expert system (PFES), anticipated to direct the manufacturing technique using an order of duties, was motivated by the need for quick manufacture of generic formulations. PFES provides a framework for new formulation system development. The specification object, which encompasses the current understanding of the formulation problem, and the formulation object, which represents the current composition of the formulation, are taken into account. This knowledge is subsequently applied to facilitate the development of the formulation. The design of later iterations of PFES involves three levels: physical, task, and control. The control level conducts the studies, while the physical level receives domain

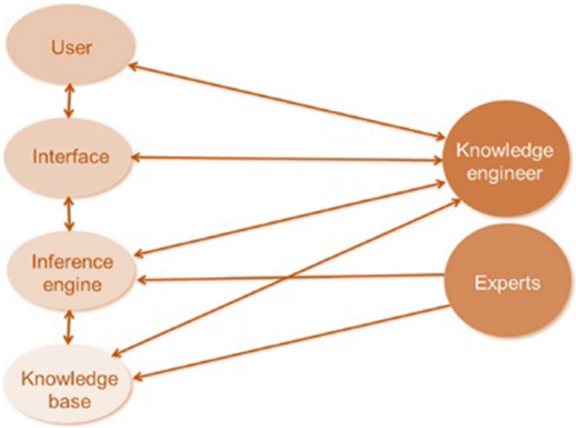

Fig. 5 Formulation of tablets and capsules uses rule-based systems

information and can be accessed from the task level through a query interface. Expert systems in formulation development have several benefits, such as ensuring a consistent process for regulatory compliance, aiding in novice and professional training, reducing product development time and cost, and freeing up experts to focus on innovation [99].

Developing innovative drug delivery methods with an eye on optimizing efficacy and avoiding adverse effects has generally taken up most of the last ten years. AI has the potential to address certain challenges associated with controlled and conventional drug delivery systems, including issues such as systemic toxicity, narrow therapeutic ranges, and dose adjustments during long-term therapy. To illustrate how AI is utilized in medicines, an example can be given where microchips are employed to manage medication administration, lower systemic toxicity, narrow the therapeutic window, and reduce adverse effects. AI has made significant advancements in enhancing the efficacy, safety, and adherence of patients by innovating implanted drug delivery devices capable of regulating drug release timing and concentration. This strategy of using AI in managing chronic diseases like diabetes, which require prompt treatment and continuous monitoring, is very advantageous. Neural networks, fuzzy logic, integrators, and differentiators have all been used to develop control systems. It is crucial to monitor glucose levels in diabetic patients and provide insulin regularly to treat the condition. As mentioned earlier, the utilization of microchips can assist in the effective management of regular blood glucose level monitoring and insulin administration. The combination of glucose sensors, mathematical models, and control algorithms holds promise for facilitating this objective. Conventional therapeutic methods that have been utilized over time face certain limitations, which can be overcome by integrating information technology, wireless communication, and ANNs into standard therapeutic procedures. As an illustration, wireless connections can be utilized to transmit orders from outside sources to units. The data from these communications are gathered and tracked to control the drug's distribution [100, 101].

Pharmaceutical manufacturing

Continual production is a valuable strategy for reducing lot-to-lot variances. The FDA recommends a non-stop processing strategy to limit the variation of final products and patient outcomes. One can use various process analytical technology (PAT) tools, efficient and cost-effective to control uninterrupted production. Through automated ML, using AI in conjunction with PAT can improve the process overall and help regulate the production process [102].

Companies that produce biopharmaceutical products can benefit from data science by integrating logistics into their processing operations. Ensuring the proper upkeep of these variables is considered a crucial regulatory consideration due to the utilization of engineered living cells in the production of biopharmaceuticals. Managing and monitoring multiple factors are necessary to maintain the purity and consistency of the manufactured product. As a result, most of the world's leading chemical businesses frequently employ big data to improve vaccine production output and keep an eye on product quality [34].

Drug synergism and antagonism prediction

When treating someone over time, studying how different drugs interact is essential. This can reduce the dose needed and prevent harmful side effects from taking multiple medications together. SnuGen utilises the master regulator inference algorithm (MARINA) to forecast synergism and antagonism. The MARINA method was established to have the ability to predict synergism with an approximate accuracy of 56%. This method clarifies the "Mater Regulator" genes which may be applied to selecting beneficial descriptors for ML techniques. One can use network-based Laplacian regularized least square methods to predict synergism and antagonistic drug interactions. As was covered in the preceding section, various AI techniques combined with medication therapy can be advantageous in multiple ways. For proper prediction, a level of confidence percentage in the range of 0.7–0.9 has been attained, comparable to the performance of the most automatic prediction system. The prediction scores obtained using the various ML techniques do not significantly differ. While ANNs, Random Forest, and SVM all have benefits and drawbacks, choosing the correct input parameters is the main issue when utilizing AI for combo therapy. One must use the parameters

that determine the quality of the prediction model when developing prediction algorithms [18].

Nanorobots for drug delivery

Integrated circuits, sensors, a power source, and a secure data backup constitute the primary components of nanorobots, which are maintained by computational technologies like AI [101]. They are designed with programming to prevent collisions, detect targets, locate and engage with them, and subsequently eliminate them from the body. Advancements in nano/microrobot technology empower them to navigate to specific locations within the body by leveraging physiological indicators like pH. This progress enhances their efficacy and reduces the occurrence of systemic side effects [103]. When creating implantable nanorobots for the controlled administration of drugs and genes, factors such as dosage customization, sustained release, and regulated release must be carefully considered. The automation of drug release necessitates the utilization of AI tools, such as neural networks (NNs), fuzzy logic, and integrators [104]. Microchip implants serve dual purposes, enabling both scheduled release of substances and precise localization within the body.

Nanomedicine

Nanomedicines merge nanotechnology and drugs to diagnose, treat, and monitor complex ailments like HIV, cancer, malaria, asthma, and various inflammatory conditions. Due to their enhanced treatment efficacy, the utilization of nanoparticle-modified drug delivery systems has experienced substantial growth in both the therapeutic and diagnostic domains [105, 106]. Combining AI with nanotechnology could solve numerous issues in product development [107, 108]. Through computational analysis, a nanosuspension of methotrexate was developed by examining the energy generated during the interaction between drug molecules and closely monitoring any conditions that could lead to formulation aggregation. Coarse-grained simulation and chemical computation can be employed to evaluate the interactions between drugs and dendrimers, as well as to analyse the encapsulation of drugs within the dendrimer structure [23].

Furthermore, researchers can investigate the impact of surface chemistry on the internalization of nanoparticles into cells using tools such as LAMMPS and GROMACS 4. The utilization of AI facilitated the development of silicasomes, which are a combination of multifunctional mesoporous silica nanoparticles loaded with irinotecan and the tumour-penetrating peptide iRGD. The inclusion of iRGD enhances the transcytosis of silicasomes, resulting in improved treatment outcomes and increased overall survival. As a result, there has been a significant three- to fourfold increase in the absorption of silicasomes [106].

Predicting the mode-of-action of compounds using AI

The prospect of an AI platform that can predict drugs' on- and off-target effects as well as *in vivo* safety profiles prior to synthesizing has medicinal chemists, in particular, thrilled. The existence of such platforms reduces the amount of time, money, and attrition rates needed to create new medications. Among these platforms are DeepTox, which predicts the toxicity of new drugs, and PrOCTOR, which assesses the probability of toxicity during clinical trials [109, 110]. If a comprehensive and precise dataset containing information on the toxicity and therapeutic characteristics of a wide range of drugs becomes available, the industry has the potential to enhance the predictive accuracy of these platforms by sharing and exchanging data.

As a substitute for chemo-proteomics, SPiDER, a novel AI tool, was recently created [111] to promote natural products for drug development. As a proof-of-concept, SPiDER was utilized to predict the molecular target of lapachone, a natural naphthoquinone with promising antitumour properties currently in clinical development. The platform expected that 5-lipoxygenase (5-LO) would be modulated allosterically and reversibly by lapachone. Through the use of a 5-LO functional test, the prediction is verified. An alternative AI methodology, known as read-across structure-activity relationships (RASAR) [112], has demonstrated the ability to effectively forecast the toxicity of unfamiliar compounds. By leveraging a vast chemical library and establishing connections between molecular structures and hazardous traits, RASAR proves valuable in this prediction process.

Conclusion and future prospect

In conclusion, the function of AI in pharmaceutical formulation and development is rapidly expanding, bringing a host of benefits to the industry. AI has already demonstrated its ability to analyse large data sets, optimize drug formulations, and streamline clinical trials. By doing so, the duration and expenses associated with drug development have been diminished, concurrently heightening the precision and efficacy of the complete process.

The prospects for AI in pharmaceutical formulation and development are up-and-coming. As AI continues to evolve and improve, it is predictable to show an even more significant function in drug development, aiding researchers in identifying new drug targets, drug interactions, and patient populations most likely to benefit from treatment.

Furthermore, as AI systems become more advanced, they can simulate biological systems more accurately,

allowing researchers to develop more personalized and effective treatments. This, in turn, will lead to more efficient and targeted drug development and personalized medicine.

So, the role of AI in pharmaceutical formulation and development has already proven to be transformative and is expected to continue to revolutionize the industry in the coming years. By leveraging the power of AI, researchers can unlock new insights into complex diseases, create more effective treatments, and improve patient outcomes on a global scale.

Abbreviations

AI	Artificial intelligence
ML	Machine learning
R&D	Research and development
ANN	Artificial neural network
CNN	Convolutional neural network
SL	Supervised learning
DL	Deep learning
GA	Genetic algorithms
QSAR	Quantitative structural activity relationship
LDA	Linear discriminant analysis
NLP	Natural language processing
MES	Model expert systems
CFD	Computational fluids dynamics
DEM	Discreet element modelling
FEM	Finite element modelling
API	Active pharmaceutical ingredients
SD	Solid dispersions
SEDDS	Self-emulsifying drug delivery system
MLR	Multiple linear regression
PFES	Product formulation expert systems
RASAR	Read across structure activity relationship

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