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ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL TECHNOLOGY AND DRUG DELIVERY DESIGN

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ABSTRACT

Artificial Intelligence (AI) focuses in producing intelligent modeling, which helps in imagining knowledge, cracking problems and decision making. In the year 1943, the first work which is now recognized as AI was done by Warren McCulloch and Walter pits. Previously, Artificial Intelligence was only limited to the field of engineering, but recently, AI plays an important role in various fields of pharmacy like drug discovery, drug delivery formulation development, marketing, management, marketing, quality assurance, 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 analyzed 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. Now the robots are using in the various medical procedures as they are more trustworthy for doctors, as they are more advanced in their work, as they can do any task within the short time period and effectively than humans. This is concluded that AI is the new evolving field in every sector, even in pharmacy, and it need more development for updating the current scenario as well as for new researches.

KEYWORDS: Artificial Intelligence, Artificial Neural Networks (ANNs), Pharmacy, Application.

INTRODUCTION

Artificial Intelligence (AI) is a stream of science related to machine learning, it focuses on intelligent computer programs, which provides results in the equivalent way to human attention process.[1] This process 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 analysing the machine learning to imitate the cognitive tasks of individual.[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. Over the past few years, there has been a drastic increase in data digitalization in the pharmaceutical sector. However; this digitalization comes with the challenge of acquiring, scrutinizing, and applying that knowledge to solve complex clinical problems.[5] This motivates the use of AI, because it can handle large volumes of data with enhanced automation.[6] 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.[7] The uses of AI models also make possible to predict the in vivo responses, pharmacokinetic parameters of the therapeutics, suitable dosing, etc.[2] AI involves several method domains, like reasoning, solution search, knowledge representation, and among them, a fundamental paradigm of machine learning (ML). Machine Learning uses algorithms which can recognize patterns within the set of data that has been further classified. There is a subfield of ML which is known as Deep learning (DL), which engages with Artificial Neural Networks (ANNs).[8] In Specific, various ANNs like Deep neural networks (DNNs), Convolutional neural networks (CNNs) and Recurrent neural networks (RNNs) controls the evolutions of AI technology. RNNs are networks with a closed-loop, having the capability to memorize and store information, such as Boltzmann constants and Hopfield networks.[9,10] CNNs are a series of dynamic systems with local connections,

characterized by its topology, and have use in image and video processing, biological system modelling, processing complex brain functions, pattern recognition, and sophisticated signal processing.[11]

In this review article, the uses of Artificial Intelligence in pharmacy, especially in drug discovery and development, drug delivery formulation development, marketing, management, marketing, quality assurance, improvising pharmaceutical industry, clinical pharmacy, hospital pharmacy and other topics are discussed.

Historical Background

In year 1943, the first work which is now recognized as AI was done by Warren McCulloch and Walter pits. They proposed the model of Artificial Neurons. Then the journey of AI has begun. In the year of 1950 Alan Turing developed the Turing Test. In 1952 the term Machine Learning was given. In 1956, The word AI first adopted by American computer scientist John McCarthy at Dartmouth conference. For the first time, AI coined as an academic field. This is known as The Birth of AI. Unimate the first Industrialist Robot joins the assembly line at General Motors and performed automated Die Casting.[12] A few years later in 1964, Eliza was introduced by Joseph Weizenbaum. Using natural language processing, Eliza was able to communicate using pattern matching and substitution methodology to mimic human conversation (superficial communication) serving as the framework for future chatter bots.[13] Then the first AI winter came during the period of 1970s. This fostered the development of The Research Resource on Computers in Biomedicine by Saul Amarel in 1971 at Rutgers University. In 1972 the first humanoid robot created by Japan named WABOT-1. These are the early enthusiasm of AI. The CASNET model is a causal–associational network that consists of 3 separate programs: model-building, consultation, and a database that was built and maintained by the collaborators. This model could apply information about a specific disease to individual patients and provide physicians with advice on patient management It was developed at Rutgers University and was officially demonstrated at the Academy of Ophthalmology meeting in 1976.[14]

A “backward chaining” AI system, MYCIN, was developed in the early 1970s. Based on patient information input by physicians and a knowledge base of about 600 rules, MYCIN could provide a list of potential bacterial pathogens and then recommend antibiotic treatment options adjusted appropriately for a patient’s body weight. MYCIN became the framework for the later rule-based system, EMYCIN. Internist-1 was later developed using the same

framework as EMYCIN and a larger medical knowledge base to assist the primary care physician in diagnosis.[15] In the year of 1982 AI came back with Expert System. Expert system was programmed that emulate the decision-making ability of human expert. In 1986, DXplain, a decision support system, was released by the University of Massachusetts. This program uses inputted symptoms to generate a differential diagnosis.[16] It also serves as an electronic medical textbook, providing detailed descriptions of diseases and additional references. When first released, DXplain was able to provide information on approximately 500 diseases. Since then, it has expanded to over 2400 diseases.[17]

In the year of 2002 AI first time entered the home in the form of Roomba, a vacuum cleaner and TUG robot were Invented which are used in Hospitals. After the year of 2010 AI grew so much with things like in 2011 IBM's Watson win a quiz and robot pharmacy was introduced in pharmacy stores, in 2012 Google launched Google Now. In contrast to traditional systems that used either forward reasoning (following rules from data to conclusions), backward reasoning (following rules from conclusions to data), or hand-crafted if-then rules, this technology, called DeepQA, used natural language processing and various searches to analyze data over unstructured content to generate probable answers.[18] This system was more readily available for use, easier to maintain, and more cost-effective. By drawing information from a patient's electronic medical record and other electronic resources, one could apply DeepQA technology to provide evidence-based medicine responses. As such, it opened new possibilities in evidence-based clinical decision-making.[19,20] In 2015 many products launched like Amazon Alexa and Google assistant. Also, in 2015 Pharmabot a chatbot developed to assist in medication education for pediatric patients and their parents.[20] In 2016 Companies like Google and Amazon started Machine Learning as Service. In 2017, Bakkar et al[21] used IBM Watson to successfully identify new RNA-binding proteins that were altered in amyotrophic lateral sclerosis. In 2018 Fast.ai releases deep learning and Google released TPU (Tensor Processing Unit) and that arehow the proliferation of AI continues. In this era AI also entered in the field of Pharmaceuticals and found useful in many places like Drug Discovery & Design, Improvising Industries, Hospital Pharmacy, Pharmacology, Drug Delivery systems etc. Software CAD (Computer aided Drug Design) is so much helpful in the drug design. Also, 3D printing of Drugs is possible through Artificial Intelligence.

Table 1: History of Artificial Intelligence.

Year	Achievements
1943	First work known as AI developed
1950	Alan Turing Developed 'Turing Test'
1952	Term 'Machine Learning' given
1956	The word AI first adopted by American computer scientist John McCarthyKnown as 'Birth of AI'
1964	Chatbot ELIZA developed
Early 1970s	Backward Chaining AI system 'MYSIN' developed
1972	WABOT-1 the first robot created by Japan
1976	CASNET model developed
Late 1970s	The First AI winter Came
1982	AI came back with Expert System
1986	DXplain a decision support system developed for information of Diseases
1987-1993	Second AI winter began
2011	Robot Pharmacy started using in stores
2012	Technology called DeepQA developed & Google Next launched
2015	Amazon Alexa & Google Assistant launched and Pharmabot a chatbot developed
2016	Companies like Google and Amzon started ML as services
2017	IBM Watson used to successfully identify new RNA-binding proteins
2018	Fast.ai released Deepl Learning& Google launched TPU

Advantages of Artificial Intelligence

1. Error minimization

AI assists in decreasing the errors and increasing the accuracy with more precision. Intelligent robots are made of resistant metal bodies and capable of tolerating the aggressive atmospheric space; therefore, they are sent to explore space.

2. Difficult exploration

AI exhibits its usefulness in the mining sector. It is also used in the fuel exploration sector. AI systems can investigate the ocean by defeating the errors caused by humans.

3. Daily application

AI is very useful for our daily acts and deeds. For example, GPS is broadly used in long drives. Installation of AI in Androids helps predict what an individual will type. It also helps in the correction of spelling mistakes.

4. Digital assistants

Nowadays, advanced organizations use AI systems like 'avatar' (models of digital assistants) to reduce human needs. The 'avatar' can follow the right logical decisions as these are emotionless. Human emotions and moods disturb judgment efficiency, and this problem can be overcome by using machine intelligence.

5. Repetitive tasks

Human beings can generally perform a single task simultaneously. In contrast to human beings, machines can perform multitasking jobs and analyze more rapidly compared to human beings. Various machine parameters, i.e., speed and time, can be adjusted according to their requirements.

6. Medical uses

In general, the physicians can assess the condition of patients and analyze the adverse effects and other health risks associated with the medication with the help of an AI program. Trainee surgeons can gather knowledge by applying AI programs like various artificial surgery simulators (gastrointestinal simulation, heart simulation, brain simulation, etc.

7. No breaks

Unlike human beings who have the capacity of working for eight h/day with breaks, the machines are programmed in such a way that they are capable of performing the work continuously for long hours, devoid of any kinds of confusion and boredom.

8. Increase technological growth rate

AI technology is widely used in most advanced technological innovations worldwide. It is capable of producing different computational modeling programs and aims for the invention of newer molecules. AI technology is also being used in the development of drug delivery formulations.

9. No Risk

In the case of working at a risky zone like fire stations, there are huge chances of causing harm to the personnel engaged. For the machine learning programs, if some mishap happens, then broken parts can be repairable.

10. Acts as aids

AI technology has played a different function by serving children and elders on a 24×7 basis. It can perform as a teaching and learning source for all.

11. Limitless functions

Machines are not restricted to any boundaries. Emotionless machines can do everything more efficiently and produce more accurately than human beings.

Disadvantages of Artificial Intelligence

1. Expensive

The launch of AI causes huge money consumption. Complex designing of the machine, maintenance, and repair are highly cost-effective. For designing one AI machine, a long period is required by the R&D division. AI machine needs to update the software programs regularly. The reinstallations, as well as recovery of the machine, consume a long time and huge money.

2. No Replicating humans

Robots with AI technology are associated with the power of thinking like humans and being emotionless. These add some advantages to performing the given task more accurately without any judgment. If unfamiliar problems arise, robots cannot decide and provide a false report.

3. No Improvement with experience

Human resources can be improved with experiences. In contrast, machines with AI technology cannot be enhanced with experience. They cannot identify which individual is hard-working and which one is nonworking.

4. No Original creativity

Machines with AI technology have neither sensitivity nor emotional intelligence. Humans can hear, see, feel and think. They can use their creativity as well as thoughts. These features are not achievable by the use of machines.

5. Unemployment

The widespread use of AI technology in all sectors may cause large-scale unemployment. Because of undesirable unemployment, human workers may lose their working habits and creativity.

Applications of Artificial Intelligence

1. Artificial Intelligence in Drug Discovery

The vast chemical space, comprising $>10^{60}$ molecules, fosters the development of a large number of drug molecules. However, the lack of advanced technologies limits the drug development process, making it a time-consuming and expensive task, which can be addressed by using AI. AI can recognize hit and lead compounds, and provide a quicker validation of the drug target and optimization of the drug structure design.[1,22] Different applications of AI in drug discovery are depicted in Figure 1. Despite its advantages, AI faces some significant data challenges, such as the scale, growth, diversity, and uncertainty of the data. The data sets available for drug development in pharmaceutical companies can involve millions of compounds, and traditional ML tools might not be able to deal with these types of data. Quantitative structure-activity relationship (QSAR)-based computational model can quickly predict large numbers of compounds or simple physicochemical parameters, such as log P or log D. However, these models are some ways from the predictions of complex biological properties, such as the efficacy and adverse effects of compounds. In addition, QSAR-based models also face problems such as small training sets, experimental data error in training sets, and lack of experimental validations. To overcome these challenges, recently developed AI approaches, such as DL and relevant modeling studies, can be implemented for safety and efficacy evaluations of drug molecules based on big data modeling and analysis. In 2012, Merck supported a QSAR ML challenge to observe the advantages of DL in the drug discovery process in the pharmaceutical industry. DL models showed significant predictivity compared with traditional ML approaches for absorption, distribution, metabolism, excretion, and toxicity (ADMET) data sets of drug candidates.[23]

The virtual chemical space is enormous and suggests a geographical map of molecules by illustrating the distributions of molecules and their properties. The idea behind the illustration of chemical space is to collect positional information about molecules within the space to search for bioactive compounds and, thus, virtual screening (VS) helps to select appropriate molecules for further testing. Several chemical spaces are open access, including PubChem,

ChemBank, DrugBank, and ChemDB. Numerous in silico methods to virtual screen compounds from virtual chemical spaces along with structure and ligand-based approaches, provide a better profile analysis, faster elimination of nonlead compounds and selection of drug molecules, with reduced expenditure.[24] Drug design algorithms, such as coulomb matrices and molecular fingerprint recognition, consider the physical, chemical, and toxicological profiles to select a lead compound.[24]

Various parameters, such as predictive models, the similarity of molecules, the molecule generation process, and the application of in silico approaches can be used to predict the desired chemical structure of a compound.[24] Pereira et al., presented a new system, DeepVS, for the docking of 40 receptors and 2950 ligands, which showed exceptional performance when 95000 decoys were tested against these receptors.[24] Another approach applied a multiobjective automated replacement algorithm to optimize the potency profile of a cyclin-dependent kinase-2 inhibitor by assessing its shape similarity, biochemical activity, and physicochemical properties.[25] QSAR modeling tools have been utilized for the identification of potential drug candidates and have evolved into AI-based QSAR approaches, such as linear discriminant analysis (LDA), support vector machines (SVMs), random forest (RF) and decision trees, which can be applied to speed up QSAR analysis.[26] King et al. found a negligible statistical difference when the ability of six AI algorithms to rank anonymous compounds in terms of biological activity was compared with that of traditional approaches.[27]

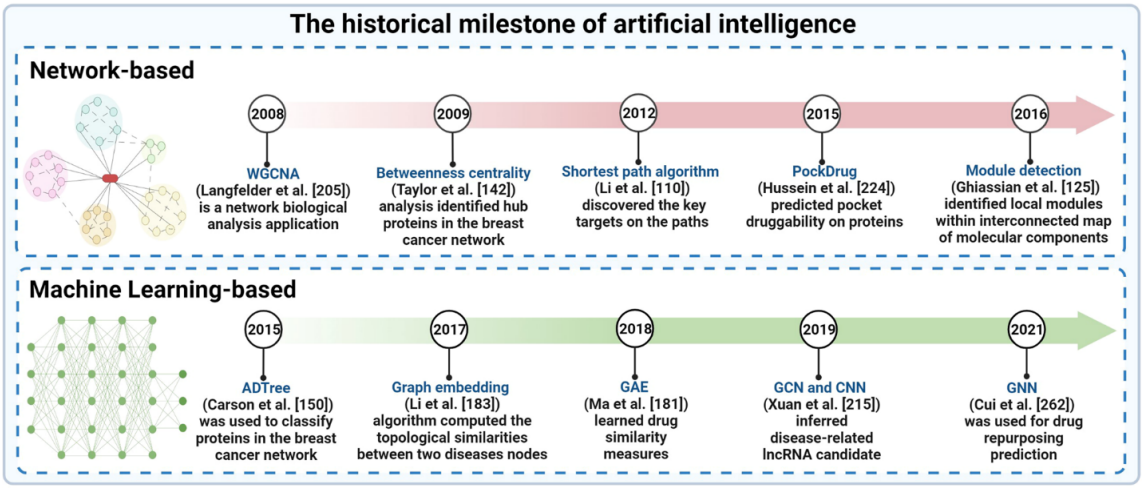

Figure 1: Artificial Intelligence in Drug Discovery.

2. Artificial Intelligence for Development of Drug Delivery System

Generally, the designing of drug delivery systems is related to some disadvantages like prediction of the relationship amongst the formulation factors and responses.[28] 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.[29] 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 various drug delivery dosage forms like, Solid Dispersions, emulsion and microemulsions, tablets, Multiparticulates (beads, microparticles and nanoparticles.[30]

a) Solid Dispersions

The ANN modeling combined with experimental design has been employed to develop solid dispersions of carbamazepine using poloxamer 188 and Soluplus®.[31] 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 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.[32] 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 a long - standing physical stability.

b) Emulsions and Microemulsions

ANNs have also been utilized for the formulation development of stable emulsions (oil/water).[33] 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 and conductance. On the basis of validation testing, ANN-predicted values were found in excellent correlation with the data obtained from the experiment.[39] ANNs have also been applied in the formulation designing of

microemulsions, where the prediction of precision based on the microemulsion nature from the formula was easily analyzed.[34] By means of the mixture of genetic algorithms and evolutionary ANNs, interior structural features and the microemulsion nature have also been forecasted with the high level of precision. In another work, an ANN modeling has been employed to forecast the formulation of stable microemulsions loaded with antitubercular drugs like rifampicin and isoniazid for oral administrations.[35] Data obtained from the constructed pseudo-ternary phase triangle-diagrams presenting the oil components and the surfactant mixture were used for the testing as well as validation of the ANN modeling.

c) Tablets

In the designing of matrix tablets, static and dynamic ANNs have been applied for the dissolution profile modeling of different matrix tablets.[36] In this work, Monte Carlo simulations and the genetic algorithms optimizer tool were applied for these modeling based on ANN algorithm. The researcher used the Elman dynamic neural networks and decision trees, which appropriately predicted the dissolution properties of hydrophilic as well as lipid-based matrix tablets exhibiting controlled drug releasing pattern. As compared to the majority of commonly employed multilayer perceptron and static networks, the Elman neural networks-based modeling demonstrated the efficient modeling of drug releasing patterns by various formula of hydrophilic as well as lipid-based matrix tablets. In a research, matrix tablets for sustained release of an antidiabetic drug, metformin HCl, was developed by means of multilayer perceptron with feed forward back propagation technique.[37] In another work, ANNs was applied for the formulation optimization of nimodipine matrix tablets for controlled releasing application.[38] A combination of ANN-based modeling and statistical optimization process has been employed for the formulation designing of glipizide releasing osmotic pump tablets.[39] A mixture of response surface methodology (RSM) and ANN-based modeling has been applied for the formulation optimization of osmotic tablets containing isradipine.

d) Multiparticulates

By employing CAD/Chem software assisted modeling, multiparticulate beads of verapamil was developed. In this work, the influences of various formulation variables as well as process variables on the in vitro verapamil releasing by the beads were analyzed. The in-vitro verapamil releasing data for the optimized beads were found to be in the line of good agreement in comparison with that of the predicted results obtained by the ANN modeling.[40]

In a work, ANN modeling was applied to assess the influence of process variables on the papain (enzyme) entrapment within alginate-based beads for the improvement of stability as well as site specific release.[41] The combination of ANN and RSM was applied to optimize alginate-based floating microspheres of aspirin, where the quantities of excipient materials, drug releasing and buoyant rate of microspheres were analyzed. ANN model was more precisely predicted in-vitro aspirin releasing pattern in comparison with that of RSM.[42] In a research, central composite design and RSM were employed for the formulation optimization of alginate methylcellulose mucoadhesive microcapsules loaded with gliclazide, where the impact of sodium alginate to methylcellulose ratio and cross-linker (calcium chloride) concentration as independent formulation variables on the drug encapsulation efficiency and drug release were statistically analyzed.[43]

3. Artificial Intelligence in Nanomedicines

Nanogel particle drug delivery system has become the novel and most important in the diagnostics and treatment as they show improved efficacy as well as bioavailability of many drugs. The working capacity can be advanced and modified by the implementation of AI.[44] A persistent challenge in all forms of drug administration is that drug synergy is time-dependent, dose-dependent and patient-specific at any given point of treatment. To overcome this challenge, the evolution towards nanomedicine-mediated co-delivery of multiple therapies has made the potential of interfacing artificial intelligence (AI) with nanomedicine to sustain optimization in combinatorial nanotherapy a reality. Specifically, optimizing drug and dose parameters in combinatorial nanomedicine administration is a specific area where AI can actionably realize the full potential of nanomedicine.[45,46] Nanoparticles can effectively stabilize and deliver synergistic combinations as demonstrated with PLGA–PEG nanoparticles encapsulating and co-localizing two different classes of agents, cisplatin-prodrug and siRNA. In the combination, the siRNA, siREV1 and siREV3L, suppress the expression of the translesion DNA synthesis (TLS) pathway, an error-prone mechanism that allows tumor cells to repair chemotherapy-induced DNA damage and predisposes the cells to develop drug-resistance. Concurrent administration of siREV1, siREV3L, and cisplatin–prodrug within PLGA–PEG nanoparticles was shown to inhibit further tumor growth and increase overall survival time in the murine models by accommodating the siRNA-mediated downregulation of TLS activity involved in acquired mutagenic drug-resistance, sensitizing the cell to the controlled release of cytotoxic cisplatin.

4. Artificial Intelligence in Prediction of Toxicity

The prediction of the toxicity of any drug molecule is vital to avoid toxic effects. Cell-based in vitro assays are often used as preliminary studies, followed by animal studies to identify the toxicity of a compound, increasing the expense of drug discovery. Several web-based tools, such as LimTox, pkCSM, admetSAR, and Toxtree, are available to help reduce the cost.[47] Advanced AI-based approaches look for similarities among compounds or project the toxicity of the compound based on input features. The Tox21 Data Challenge organized by the National Institutes of Health, Environmental Protection Agency (EPA), and US Food and Drug Administration (FDA) was an initiative to evaluate several computational techniques to forecast the toxicity of 12707 environmental compounds and drugs; an ML algorithm named DeepTox outperformed all methods by identifying static and dynamic features within the chemical descriptors of the molecules, such as molecular weight (MW) and Van der Waals volume, and could efficiently predict the toxicity of a molecule based on predefined 2500 toxicophoric features. The different AI tools used in drug discovery are listed in Table 2.

SEA was used to evaluate the safety target prediction of 656 marketed drugs against 73 unintended targets that might produce adverse effects.[48] Developed using an ML-based approach, eToxPred was applied to estimate the toxicity and synthesis feasibility of small organic molecules and showed accuracy as high as 72%.[49] Similarly, open-source tools, such as TargeTox and PrOCTOR, are also used in toxicity prediction.[50] TargeTox is biological network target-based drug toxicity risk prediction method that uses the guilt-by-association principle whereby entities that have similar functional properties share similarities in biological networks. It can produce protein network data and unite pharmacological and functional properties in a ML classifier to predict drug toxicity.[51] PrOCTOR was trained using a RF model and took into account drug-likeliness properties, molecular features, target-based features, and properties of the protein targets to generate a 'PrOCTOR score', which forecasted whether a drug would fail in clinical trials owing to its toxicity. It also recognized FDA-approved drugs that later reported adverse drug events.[52] In another approach, Tox_(R) CNN involving a deep CVNN methods evaluated the cytotoxicity of drugs that had been exposed to DAPI-stained cell.[53]

Table 2: Artificial Intelligence Tools used in Drug Discovery.

Tools	Details
DeepChem	MLP model that uses a python-based AI system to find a suitable candidate in drug discovery
DeepTox	Software that predicts the toxicity of total of 12000 drugs
Deep Neural Net QSAR	Python-based system driven by computational tools that aid detection of the molecular activity
ORGANIC	A molecular generation tool that helps to create molecules with desired properties
Potential Net	Uses NNs to predict binding affinity of ligands
Hit Dexter	ML technique to predict molecules that might respond to biochemical assays
DeltaVina	A scoring function for rescoring drug–ligand binding affinity
Neural graph fingerprint	Helps to predict properties of novel molecules
AlphaFold	Predicts 3D structures of proteins
Chemputer	Helps to report procedure for chemical synthesis in standardized format

5. Artificial Intelligence in Polypharmacology

Nowadays 'One disease multiple targets' concept governs over the 'one-disease-one-targets' concept for the advanced realization of pathological process in various disorders at their molecular basis. The phenomenon of 'one-disease-multiple-targets' is known as Polypharmacology.[54] Polypharmacology is emerging as the next paradigm of drug discovery. The Polypharmacological approaches aim to discover the unknown off targets for the existing drugs (also known as drug repurposing).[55] There are numerous and useful databases, for example, PubChem, KEGG, ChEMBL, ZINC, STITCH, Ligand Expo, PDB, Drug bank, Super Target, Binding DB which are accessible for the accomplishment of a variety of important and useful information related to the structure of crystals, chemical

features, biological properties, molecular pathways, binding affinities, disease concern, drug targets, etc. AI also helps to discover the databases to sketch Polypharmacological molecules/agents. AI has bigger potential for vital developments in medicine disorders and has achieved smart performance in AD detection.[56]

6. Artificial Intelligence in Clinical Trial Planning

The new drug discovery clinical trials are done for specific disease or infection with the purpose of building or checking safety and efficacy of a particular drug and it requires at least 6 to 10 years with a considerable money investment in completion and the chances of success are less there, which leads to huge loss of industry as well as investor.[57] There are many reasons of failure including shortage of technical arrangements as well as unsuitable patient selection. These losses can be minimized with execution of AI in clinical trials which provides a vast digital data for access.[58] The main step in the clinical trials is the appropriate selection of the patients which takes about 33% of total time and the success rate can be ensured by the correct selection of the patients, if this step is taken wrong then leads to 86% or overall failure of trails. AI can help in choosing the patient data on the basis of patient specific gene-exposome profile examination for the phase II and III of a specific disease clinical trial which will results in the early expectations of drug target in selected patients.[71] There is a problem of patients who give up at the time of clinical trials, this problem makes the selection process more sensitive otherwise it leads to 30% failure of the clinical trials as well as time and money. This failure may be minimized by keeping close eye on the patient nursing and help them to monitor the rules related to clinical trial.[59] A mobile application was established by AI Cure which is responsible for the close monitoring of regular medication consumption in Phase II trials by patients who are suffering from schizophrenia. This application increased the patient loyalty up to 25% towards the clinical trial and ensuring the success of clinical trial.

7. Artificial Intelligence in Primary and Secondary Drug Screening

Today AI has come out as a very successful and demanding technology because it saves time and is cost-efficient. In general, cell classification, cell sorting, calculating properties of small molecules, synthesizing organic compounds with the help of computer programs, designing new compounds, developing assays, and predicting the 3D structure of target molecules are some time-consuming and tiresome tasks which with the help of AI can be reduced and can speed up the process of drug discovery.[60] The primary drug screening includes the

classification and sorting of cells by image analysis through AI technology. Many ML models using different algorithms recognize images with great accuracy but become incompetent when analyzing big data. To classify the target cell, firstly, the ML model needs to be trained so that it can identify the cell and its features, which is basically done by contrasting the image of the targeted cells, which separates it from the background.[61] Images with varying textured features like wavelet-based texture features and Tamura texture features are extracted, which is further reduced in dimensions through principal component analysis (PCA). A study suggests that least-square SVM (LS-SVM) showed the highest classification accuracy of 95.34%. Regarding cell sorting, the machine needs to be fast to separate out the targeted cell type from the given sample. Evidence suggests that image-activated cell sorting (IACS) is the most advanced device that could measure the optical, electrical, and mechanical properties of the cell.[62]

The secondary drug screening includes analyzing the physical properties, bioactivity, and toxicity of the compound. Melting point and partition coefficient are some of the physical properties that govern the compound's bioavailability and are also essential to design new compounds[63], while designing a drug, molecular representation can be done using different methods like molecular fingerprinting, simplified molecular-input line-entry system (SMILES), and Coulomb matrices.[64] These data can be used in DNN, which comprises two different stages, namely generative and predictive stage. Though both the stages are trained separately through supervised learning, when they are trained jointly, bias can be applied to the output, where it is either rewarded or penalized for a specific property.[65] This whole procedure can be used for reinforcement learning. Matched molecular pair (MMP) has been extensively used for QSAR studies. MMP is associated with a single change in a drug candidate, which further influences the bioactivity of the compound.[66] Along with MMP, other ML methods are used like DNN, RF, and gradient boosting machines (GBM) to get modifications. It has been observed that DNN can predict better than RF and GBM.[67] With the increase in databases, which are publicly available like ChEMBL, PubChem, and ZINC, we have access to millions of compounds annotating information like their structure, known targets and Purchas ability; MMP plus ML can predict bioactivity like oral exposure, intrinsic clearance, ADMET, and method of action. Optimizing the toxicity of a compound is the most time-consuming and expensive task in drug discovery and is a crucial parameter as it adds signifcant value to the drug development process.

8. Artificial Intelligence in Pharmaceutical Manufacturing

The involvement of AI in manufacturing is like power boost for the pharmaceutical industry. The AI is continuously changing the manufacturing process, as now modern manufacturing systems with AI are trying to give human knowledge to machines with expanding interest of efficiency and better product quality along with reducing the complexities in the manufacturing processes. AI platforms are making the manufacturing process so easy with the advanced tools like CFD, Reynolds Averaged Navier-Stokes solvers technology that use to review the stress level in machine and misusing the automation in the many pharmaceutical process. In the similar way, mathematical simulations are also producing a progressed ways to deal with complex flow problems in manufacturing.[68]

It has been used in the manufacturing of many compounds like sildenafil, diphenhydramine hydrochloride with the maximum yield and purity as similar as convectional method of manufacturing. The working capacities of granulation has increased up to 600L with the aid of AI technologies and correlated neuro-fuzzy logic. They provide prediction with the help of an equation which determines the quantity of fluid to be added and necessary speed for the granulating machine, as well as the diameter of granules.

9. Artificial Intelligence in Quality Control[69]

The equilibrium of various factors should be maintained in the manufacturing of the product from the crude material.[70] The back-to-back consistency and Quality control tests on the products are required to maintain for the desired product. These methods probably won't be the best methodology for each situation, so that there is a requirement of AI implementation. Gohel et al. considered the dissolution rate profile as an indicator of consistency for batch-to-batch operations with the help of artificial neutral network (ANN), that predict an error of <8% in the dissolution rate of various batch to batch operations. AI can be executed for the guidelines of processes manufacturing to accomplish the product. Gams et al. used an AI system which is a collaboration of both human efforts and AI where the primary or preliminary information were analyzed from the various batches and the results from them are kept as prove which were additionally converted into guidelines and examined by various operators to lead the manufacturing set in the future. There are many computerized platforms which are used to ensure the quality of the product.[71] E.g., Electronic Lab Notebook. With use of data mining and various intelligent techniques in the TQM (Total Quality

Management), improves the important methodologies during the complex decision, creating new technologies for the advanced quality product.[72]

10. Artificial Intelligence in Product Management[73]

Market positioning of product is defined as the mode of building a marketing value or recognition of a product in market where it attracts buyer to buy them. It tries to make a vital element in practical strategies in business for encouraging organizations to make their own matchless personality among all products. The same methodology was followed by a company in the marketing of pioneer brand Viagra, and they focused on other aspects associated with the men's erectile dysfunction but not specifically on the treatment. It has become easier for companies to market their products and get a unique marketing value of their company using the AI strategy plus e-commerce sites for advertisement. Companies are using 'Web Crawlers' as one of the innovative AI platforms for getting a marketing value in online market and help to make a vital element in the market. Companies are trying to make their websites better than their competitors and offering reward system for a short time period which affect their market sale and make them popular.[58]

11. Artificial Intelligence in Market Advice and Analysis

The nonstop growth of business results in the success of a company. The results of R&D department with the considerable access to technologies, is facing failure due to the lack of the new marketing strategy. The advanced digital technologies are helping in the digital marketing by applying multi criteria decision-making approach which helps in the collection and examination of the statistical and mathematical data and developing an AI based decision making models by involving human inference with the general goal of building new advertising strategies.[74]

AI also work like a decision-maker which gives the new marketing strategy for a product depending on the customer's perspective and understanding the need of the market and ultimately results in the huge marketing of product. AI-based software's with the executive of ML observe the customers' history based on the last experience, and show the advertisements of products on different sites or platforms which will directly address to the commercial site of product by just a click. This method works on the natural language-processing tools that examines the words entered by you and relate them to the different probable products in the market. Several companies are allowing the searching of products in the web by using product's characteristic, specification and their brand name; this makes the market of a

product by its work. In the similar way, many pharmaceutical companies are launching their apps and making sites for the digitalization e.g., 1 mg, pharmeasy etc. AI can predict the market situation for various essential pharmaceutical products which helps companies to keep their price, stock as per the market consuming capacity and reducing the loss. Example of AI platform for such work: Smart Sales Prediction Analysis.[75]

Why Artificial Intelligence in Pharmacy is a good Idea?

 Pharmaceutical Industry can accelerate innovation by using technological advancements.

 The recent technological advancement that comes to mind would be artificial intelligence, development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages.

 An estimate by IBM shows that entire Healthcare domain has approx. 161 billion GB of data as of 2011.

 With humongous data available in this domain, artificial intelligence can be of real help in analyzing the data and presenting results that would help out in decision making, saving Human effort, time, money and thus help save Lives.

 Epidemic outbreak prediction; using machine learning /artificial intelligence one can study the history of epidemic outbreak, analyze the social media activity and predict where and when epidemic can affect with concealable accuracy.

 AI can design new Drugs and drug combinations.

 Deliver clinical trials within minutes.

 Drugs which are not tested on humans and animals can be tested on the virtual models that are engineered to mimic physiology of organs.

 Robots help in manufacturing of medication as well as distribution.

 Block chain technology will handle the distribution of the drugs.

 Local pharmacist can 3D print the drugs.

Challenges to Adoption of Artificial Intelligence in Pharma

1. The unfamiliarity of the technology

For many pharma companies, AI still seems like a “black box” owing to its newness and esoteric nature.

2. Lack of proper IT infrastructure

That's because most IT applications and infrastructure currently in use weren't developed or designed with artificial intelligence in mind. Even worse, pharma firms have to spend lots of money to upgrade their IT system.

3. Breaking down data silos and streamlining electronic records

Much of the data is in a free text format, and the data management is messy and unorganized across the heterogeneous databases. This means that pharma companies have to go above and beyond to collate and put this data into a standard form that can be analyzed.

4. Low accuracy of the training data

Even though algorithms have a higher threshold for minimizing errors, there are still some categorical errors from training sets.

5. Overfitting or underfitting

With algorithm prediction, there is a concern with overfitting or underfitting. Overfitting means when a model consists of lower quality information/technique but generates higher quality performance. Underfitting models fail to recognize the underlying trend in the datasets and generalize the new data. Both result in inaccurate results.

6. Data quality, governance, security, and interoperability

Issues around data will always be at the heart of successfully promoting AI solutions. Healthcare is the least digitized sector, which needs to take a systematic approach to develop common data standards and processes to maximize the value of existing data. Healthcare providers and AI companies need to put in place robust data governance, ensure interoperability and standards for data formats, enhance data security and bring clarity to consent over data sharing.

7. The need for transparent algorithms to meet drug development regulations

Transparency in healthcare is quite a task given the complexity of the processes involving AI.

8. Hesitant to change

Pharma companies are known to be traditional and resistant to change.

Optimization of formulation using ANN

Design of new network help in, making choice of the Self organizing feature maps (SOFMs)

network model.[29] To forecast the output responses use of the functions like TanhAxon, SigmoidAxon, LinearTanAxon, Linear SigmoidAxon, and Axon can used.[30] Differing activations task can be presented by performance parameters like mean squared error (MSE), minimum absolute error, correlation coefficient and predicted output of the selected network models.[31]

1. **Partnerships between artificial intelligence (AI) and pharmaceutical companies and areas of collaboration in drug development.[32]**

Table no 3: Partnerships of artificial intelligence (AI) and pharmaceutical companies and areas of collaboration in drug development.

SR.NO	PHARMA	AREA OF COLLEBRATION	ARTIFICIAL INTELLIGANCE
1	Astellas pharma	Drug repurposing	Biovista
2	Bayer pharma	To track real-time data via smartphones and other wearable technologies	Xbird
3	Roche	to target personalized medicine using medicine learning and large scale genome sequencing.	Bina
4	Sumitomo dainippon Pharma	To identify diseases new tratments for psychiatric	Exscientia
5	GlaxoSmithKline	To discover novel and selective small molecule	Exscientia
6	GlaxoSmithKline	To identify novel biological target and pathway	Insilico medicine
7	Abbvie	To announce the mechanism of AI based patient monitoring platform can improve adherence.	AiCure

PROGRAMING LANGUAGES USED IN A.I

Table no 4: PROGRAMING LANGUAGES USED IN A.I

SR NO	LANGUAGE	USES
1	Python	Most Effective language for A.I, Machine learning and A.I algorthms can easily implimented,
2	Prolog	Used in knowledge based and expert system, Pttern matticching, Prebase data structuring, Automatic Tracking. Use in medical project.
3	Java	Simplified work with large scale project, good user interaction, use for making graph and interfaces.
4	Lips	Oldest and most suited for A.I, Develop by father of A.I, Capable of processing symbolic information, Create Dynamic object easily.
5	R	Statistical Programming language, analysing and manupulating data for statistical purpose, Produce methamathical symbol.

CONCLUSION

The human is believe to be the most complex and cultured machine, but now, the situation has changed significantly. Human are no longer defined to be the most complex machine, the human brain is doing hard word to develop a system that is more complex and effective than human in working capacity and it has successful in doing so. Now it has become an essential part in the pharmaceutical industry in addition to health care system and the researchers are on the fact of implementing the AI in every field of so that many researches are being carried out globally to enhance the manufacturing process better, and enhancing other activities in industry as well as hospitals. The tools of AI like Watson for oncology, Erica robot, robotic pharmacy, etc. has been reformed the pharmacy professional, making it automatic as well as increasing working capacity at a much great extend and there are the less risks of errors. The aim of implementing AI in pharmaceutical is to decrease challenges which met in companies like increased cost of drug development etc. AI is also speeding up the needed time for the development and design as well quality, efficacy, and safety of product in the cost effective manner, which is turns in the more startups in this field. However, execution of AI in the system is not intended to replace the humans but they are intended to help human and work under the guidance of humans. However, if we look at the unemployment ratio as it is increasing day by day and will increased more after the implementation of AI, then it forced to rethink otherwise all the activities that are done by humans, will be a part of AI executive.

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