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An Innovative Platform for Designing Novel Drug Formulations Supported by Artificial Intelligence

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ABSTRACT :

AI significantly improves drug discovery by finding compounds quickly, confirming targets, simplifying drug structures, and prioritizing response templates. It covers applications in clinical trials, pharmacovigilance, drug safety, and novel drug formulation and delivery. AI and nanotechnology could change targeted therapies, making them more effective and reducing side effects. In this review paper, we explore the potential applications of Artificial Intelligence (AI) in the pharmaceutical sector, focusing on medication administration and development with nanotechnologies and nanomedicines. We address issues related to privacy, data security, the interpretability of AI models, regulatory issues, and the challenges associated with AI in the pharmaceutical sector. It also concludes with a discussion of future perspectives, new trends, AI model limitations, biases, and the importance of cooperation and knowledge exchange to revolutionize the pharmaceutical sector and enhance patient care.

Keywords: Artificial Intelligence, Pharmaceutical sector, Novel drug formulation, Nanotechnology

1. INTRODUCTION :

Artificial Intelligence (AI)

The computerized representation of human intelligence is known as artificial intelligence (AI). AI includes gathering data, establishing guidelines for using it, evolving to provisional or firm findings, and self-correction [1]. Experts establish AI as a solution to problems involving numbers and data. Tremendous technological developments in almost every industry, including engineering, architecture, education, accounting, business, health, and more, emerged from this discovery. AI has made significant advancements in the healthcare industry by handling and preserving data and information. AI has transformed the healthcare industry, making it more effective and efficient, and the pharmaceutical industry is no exception [2]. A specialized area of computer science called artificial intelligence (AI) allows machines to operate effectively and interpret complicated data. The integration of AI technologies in pharmaceuticals has led to accelerated drug discovery processes, enabling researchers to analyse vast datasets and identify potential compounds more quickly than traditional methods. Predictive analytics powered by AI can also improve the designs of clinical trials, making it easier to choose the right patients and raising the chances of success [3].

AI in the Pharmaceutical

AI has become an influential tool that uses human knowledge to solve difficult problems quickly. Major advancements in artificial intelligence and machine learning represent a revolutionary prospect for pharmaceutical dosage form testing, formulation, and drug discovery. Researchers can find disease-associated targets and identify how they will interact with possible treatment options by using AI algorithms that evaluate vast amounts of biological data, such as proteomics and genomics. This increases the possibility of successful drug approvals by enabling a more focused and effective approach to drug research. Additionally, by streamlining research and development procedures, AI can help lower development costs. In addition to predicting the pharmacokinetics and toxicity of potential drugs, machine learning techniques assist in the design of experiments. By prioritizing and optimizing lead compounds, this capability lessens the need for expensive and time-consuming animal testing. Artificial intelligence (AI) algorithms that evaluate accurate patient data can improve therapeutic results and compliance among patients for customized medical programs. There is discussion of a number of AI-based pharmaceutical technology methods, along with their advantages and disadvantages. There are promising opportunities to improve patient care and drug development procedures with their ongoing investment in and research into AI in the pharmaceutical sector [4].ere introduce the paper, and put a nomenclature if necessary, in a box with the same font size as the rest of the paper. The paragraphs continue from here and are only separated by headings, subheadings, images and formulae. The section headings are arranged by numbers, bold and 9.5 pt. Here follows further instructions for authors

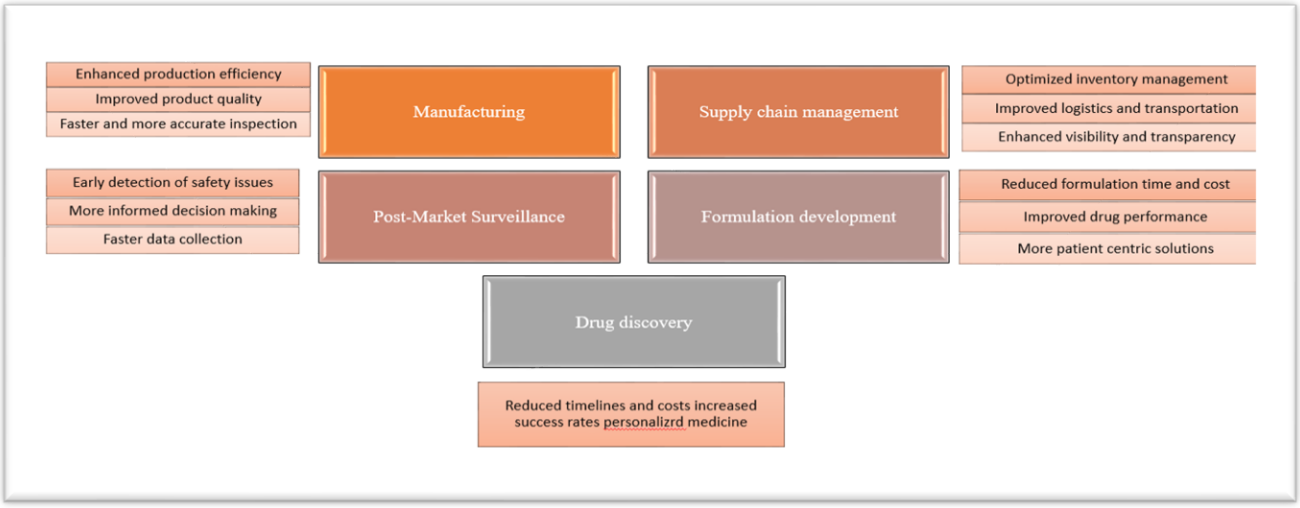

Fig.1 Artificial Intelligence assisting Drug Lifecycle

NOVEL DRUG FORMULATION

In addition to conventional dosage forms, pharmaceutical sciences have observed the development of other formulations, like pellets, extrudes, solid dispersions, nanoparticles, and liposomes. Because AI applications in formulation techniques can effectively address a range of API issues, including low solubility, stability, bioavailability, and production capability, it is even more worthwhile to research these methods in order to develop next-generation drug products with desired efficacy and health outcomes [5]. Many people believe that taking drugs orally is the most practical and ideal way to administer medications. In contrast to traditional immediate-release formulations of the same drug, the creation of oral extended-release modified-release dosage forms has become a widely accepted approach. These formulations offer a prolonged release of the drug over an extended period of time, improving patient compliance and bioavailability and the resulting blood concentration-time profiles of medications that otherwise have few limitations [6]. Extended-release medications have recently become a very useful tool in medicine, offering patients a number of tangible and intangible advantages. Among all drug delivery methods, due to its convenience, oral administration is the most often used method for various pharmacological compounds, which improves patient compliance. As a result, oral extended-release drug delivery systems show great promise for oral medications with high dosage frequency and short half-lives. Extended release offers a way to lessen pharmacological side effects by preventing the therapeutic concentration of the medication from changing in the body. In terms of drug delivery mechanisms, oral extended-release medications will remain the most common. In addition to increasing patient comfort and compliance, an extended-release product will maximize a drug's therapeutic impact and safety [7].

USE OF AI IN DIFFERENT NOVEL DRUG FORMULATIONS

1. Immediate-Release Tablets Formulation

Turkoglu created a direct compression tablet formulation using hydrochlorothiazide to increase tablet strength [8]. To explain the characteristics of the granules and tablets (disintegration time, hardness, and friability), processing variables (granulator type, binder addition technique). Neural networks outperformed conventional statistical techniques, as these two investigations showed. As a result, researchers have re-examined Kesavan and Peck's findings using a range of neural networks and genetic algorithms [9]. This presentation demonstrated how the optimal formulation was decided by the constraints imposed on the several tiers of components and processing variables, as well as the relative importance of the output attributes [10]. The same data was analysed by researchers using neuro-fuzzy computing, and they often developed useful rules that emphasized the salient features of every given item [11].

2. Hard Gelatine Capsule Shell Formulation

Formulations of Hard gelatine capsule are developed using various techniques such as expert systems and artificial neural networks. Human mental functions like Artificial neural networks (ANNs) promote learning, generalization, abstraction from domain knowledge, and prediction. The maker can foresee the characteristics of the theoretical preparation or develop a few domain-specific tactics for future events by using artificial neural networks (ANNs) to quickly turn the facts and statistics gathered during investigative work into knowledge [12]. Researchers used a new dataset to retrain the ANN, and the results showed models with an R2 of less than 70%. Finally, the smart hybrid system estimated that about 5% of the model medications would be soluble. The researchers showed that by cross-validating only 10% of the newly generated data, the system could construct a formulation that satisfied its performance requirements. By taking into account wettability and inherent dissolving qualities, researchers demonstrated the system's capacity to analyse a number of BCS class II medications [13].

3. Solid Dispersions (SD)

Solid dispersions are defined as one or more APIs distributed inside a solid matrix [14,15]. They are currently a useful and reasonably priced method of improving bioavailability and solubility [16]. Both business and academia have made extensive use of them to solve problems with APIs' poor solubility. ANNs have been utilized to optimize the formulations in numerous AI-based SD investigations [17, 18, 19]. To improve the floating and drug release

properties of SD of Nimodipine made with PEG and effervescent mixes, researchers used artificial neural networks (ANNs) [20]. In an SD made using PVP, ANNs were used to clarify the interaction between factors including temperature, PEG molar mass, and API concentration [21]. The stability of SD can be predicted; researchers have created a model employing machine learning techniques. They compared eight machine learning techniques using twenty molecular descriptors. The RF model offered insights into each input and showed the highest estimate precision among these techniques. Out of the twenty descriptors they selected, the drug loading ratio, relative ambient humidity, storage temperature, preparation temperature, and molecular weight of polymers were the top five contributing parameters [22].

4. Emulsions, Microemulsions, and Nanoemulsions

Water and oil phases are dispersed over one another in emulsions, which are biphasic systems stabilized by an emulsifier [23]. Numerous benefits, such as enhanced API bioavailability, exceptional optical clarity, and enhanced long-term stability, could result from the use of micro- and nanoemulsions [24,25,26,27]. Studies on these systems using AI techniques have been published by researchers. In order to create a stable o/w emulsion, Kumar et al. used ANNs to control the amount of fatty alcohol. The characteristics of the emulsion products that the ANNs could reliably predict included conductivity, viscosity, zeta potential, and particle size. Additionally, they enabled the quantification of the inputs' relative importance [28]. By developing two artificial neural networks (ANNs) that can identify the type of microemulsion based on either a differential scanning calorimetry (DSC) curve or the intended composition, Gasperlin et al. were able to accurately predict the structures of microemulsions [29]. Furthermore, Agatonovic-Kustrin et al. used ANN model data to create a stable microemulsion formulation for oral delivery of isoniazid and rifampicin to treat the continuing stage of tuberculosis [30]. Amani et al. employed ANNs to investigate possible factors on nanoemulsion particle size and found that the total energy supplied during preparation was the most significant factor in the final particle size [31]. Seyed et al. also investigated the nanoemulsion's component concentrations in an effort to identify the most stable structure with the least amount of cytotoxicity. They discovered that cytotoxicity was unaffected by emulsifier concentration, which was shown to be the main factor influencing nanoemulsion stability [32].

5. Pharmaceutical Powder

Farizhanidi and colleagues investigated the development of a dry powder carrier that is inhaled using machine learning (ML). The study employed 65 datasets, each comprising three drugs and three carriers. SEM pictures were used as input variables for the database, including Critical Material Attributes (CMAs) and quantitative characteristics such as mean polar facet orientation (FPO), skewness of the evaluated profile (Rsk), and root mean square deviation (Rq). Both the emitted dosage (ED) and fine particle fraction (FPF) were utilized as outputs. A feed-forward ANN model was devised for modelling purposes. For training, fifty subsets of the database were employed, and for testing, fifteen subsets. Compared to empirical modelling, the model demonstrated a considerable improvement in accuracy and precision, with R 2 values 0.9820 and 0.9556 for ED and FPF, respectively. The feasibility of using AI technologies to develop dry powder inhalation products was demonstrated in this work [33].

Bioactivity of peptides as well as stability were examined by Chauhan et al. in relation to a number of drying techniques, like freeze-drying (FD) and spray drying (SD). The present study employed an artificial neural network (ANN) model to forecast anti-inflammatory bioactivity, along with peptide activity, following the first processing of the rice natural peptide network (NPN) by both SD and FD. The outcome showed that there was no appreciable distinction between the different drying methods, with the estimators showing up to 85% accuracy in determining anti-inflammatory activity [34]. Using AI models based on ANN and SVM, Keskes et al. examined the drying kinetics. The impact of several important factors on drying time, such as drying temperature, initial mass, water content, and drying pressure, was also examined. With a R 2 of 0.999 and an RMSE (Root Mean Square Error) of less than 8.810405 × 10 -3, the AI models showed accurate prediction [35]. showed that the estimators had an accuracy of up to 85% when evaluating anti-inflammatory activity, and that there was no appreciable difference between the different drying methods [36]. Keskes et al. investigated the drying kinetics using AI models based on ANN and SVM. They also looked at the effects of key variables on drying time, including drying temperature, initial mass, water content, and drying pressure. With a R 2 of 0.999 and an RMSE (Root Mean Square Error) of less than 8.810405 × 10 -3, the AI models showed accurate prediction [37].

6. Granules

Zhao et al. used AI algorithms to evaluate and predict medication concentrations in sugar-free granules. Study show that near-infrared (NIR) spectroscopy can be used to assess the amount of API in granules. The remaining medication was then predicted using a variety of machine learning techniques based on the NIR spectra. The last three AI techniques that were optimized for modelling development were the evolutionary algorithm, particle swarm optimization (SVM), and backpropagation artificial neural networks (ANN). The results demonstrated that AI models are practical instruments for measuring the concentration of medications in granules [38]. Using an AI technique that coupled neuro-fuzzy logic with gene expression programming, Landin examined the ideal impeller power during high shear wet granulation processing. The modelling approach employed included the following input variables: volume, wet mass density, mean torque, liquid ratio, impeller diameter, speed, and volume. The prediction results shown a high correlation (R 2 > 86.78%) for many batches with capacities ranging from 25 L to 600 L. Furthermore, the results have shown the great potential to predict the final impeller power and so calculate the endpoint of the high-shear granulation process [39].

7. Tablets

The ability of CNNs to identify internal tablet defects was identified by Ma et al. For this investigation, many excipients containing tablets batches like microcrystalline cellulose and mannitol were made, and an X-Ray Computed Tomography (XRCT) equipment used to take pictures of tablets. The number of photographs increased from 573 to 43,548 using a picture augmentation technique. Three CNN modules were used for the picture analysis: Module 2 identifies individual tablets by an algorithmic analysis; UNet A extracts the pills from the bottle; and UNet B measures internal tablet fractures. During the model testing, the UNet neural network showed up to 94% accuracy for seven batches of tablets. Furthermore, this CNN technique may significantly save time, workload, and cost and aid in the discovery of defects in other products [40].

8. Tablets with 3D printing

Obeid et al. used the ANN model to examine how processing variables and the tablet surface area/volume ratio affected the drug release from diazepam tablets that were 3D printed. For this study, which sought to determine the dissolution rate, processing features such as an infill density and infill pattern that ranges between 20% and 100% were regarded as input variables. The earliest application of self-organizing maps (SOM) was to visualize and understand the interplay of numerous variables. Following SOM analysis, the surface area/volume ratio and infill density were chosen as input variables for additional modelling research. They then constructed a three-layer artificial neural network (ANN) for modelling, with two neurons in the first layer, three hidden neurons in the second layer, and five neurons in the third layer. High dissolution rates were attained with a diagonal infill pattern and a decreased infill density after ANN modelling and validation. The dissolution pattern of the disodium diazepam tablet was accurately predicted by the ANN model [41]. Author evaluated the viability of identifying defects in tablets manufactured using selective laser sintering 3D printing technology using CNN. A number of CNN pre-trained models, including Exception and VGG16, were applied to this image classification job. According to the results, VGG16 had the highest accuracy, at 95.8%. Additionally, VGG16 demonstrated more precise effect localization than Exception, and Grad-CAM effectively demonstrated and illustrated the CNN model [42].

9. Capsules

It has been shown by Zhou et al. that an improved CNN may be used to identify capsule defects. Handmade capsules with a variety of flaws, including shrivelled, locked, or nested capsules, oil stains, concave heads, uncut bodies, and perforations, were used in this study. They utilized capsules. The model's overfitting was mitigated by using the Adam optimizer and the enhanced CNN's L2 regularization. For comparison, K-Nearest Neighbour (KNN) and SVM were used. Using this enhanced CNN model, the confusion matrix results showed up to 97.56% accuracy in detecting capsule flaws [43].

10. Emulsions

Stable formulations of oil-in-water emulsions have also been produced using ANNs. When optimizing the fatty alcohol concentration to create oil/water emulsions, the unreliable variables (factors) were the lauryl alcohol concentrations and time. The variables that yielded reliable results were droplet size, zeta potential, conductance, and viscosity. Validation tests revealed that ANN-predicted values were highly correlated with the outcomes of the trial [44]. An ANN model was developed to predict stable microemulsion formulations for oral delivery, including isoniazid and rifampicin. Data from several pseudo ternary phase triangles containing a combination of oil and surfactant components were utilized to train, test, and validate the ANN model [45].

11. Modified Release-based Drug Delivery

a. Matrix Tablets

Artificial neural networks (ANNs), both dynamic and static, were used in matrix tablet design to model the dissolving characteristics of matrix tablets. The genetic algorithm optimizer tool and Monte Carlo simulations were employed in this work for these ANN-based modelling. Unlike most often used MLP and static networks, the Elman neural networks-based modelling demonstrated the successful modelling of drug-releasing patterns by different formulations of hydrophilic and lipid-based matrix tablets [46]. CMA and Process Analytical Technology (PAT) output data were also combined to generate a modelling database. Among the most important factors for the model's prediction, according to the results, was the particle size distribution (PSD). Furthermore, ANN was demonstrated to be the best accurate model out of all of them based on the evaluation metrics [47]. Han et al. investigated the use of neural networks with deep layers to predict when pills will disintegrate. In this work, the data from 145 drug formulations were divided into training and testing subsets using the modified maximum dissimilarity technique. The significant advanced data selection method may be demonstrated by the data sets utilized for testing and validation. Ten hidden layers and fifty neurons in each layer comprised the DNN that was constructed for the modelling procedure. The testing and validation sets showed that the improved DNN had high accuracies of 85% and 80%, respectively. Consequently, tablet medication release characteristics have been successfully predicted using ML models [48]. In order to develop controlled release formulations of clopidogrel, the effect of tablet components on release characteristics has also been investigated using the fuzzy logic method and ANN analysis [49].

b. Implants

The formulation parameters and the profile of dexamethasone release from the cochlear implant coatings were predicted using an artificial neural network (ANN) model. The ability of the ANN model to identify the ideal levels of formulation parameters was assessed in order to provide the best potential medicine release profile. Not only did the ANN model expedite the formulation design process, but it also successfully modelled the implant device's drug release profile. The results were comparable to those obtained experimentally, indicating the efficacy of the model [50].

c. Suppositories

The layered excipient suppositories' slower and faster paracetamol release has been compared using an ANN technique in conjunction with modelling and simulation of the compartment-based models. It has been found that the absorption-increasing effect of mono-di-glycerides and the hepatic bypass mechanism combine to increase the degree of medication absorption [51].

12. Microsystem-based Drug Delivery

a. Beads, Pellets, and Microspheres

In order to improve stability and site-specific delivery, the impact of process variables on papain entrapment in cross-linked alginate beads has been evaluated using an ANN model. After being tested for both accelerated and long-term stability, papain entrapped in alginate beads had a noticeably longer shelf life, proving the usefulness of ANN technology for producing stable beads that might potentially deliver medications to specific locations [52]. It has been demonstrated that the pH of the external aqueous phase significantly affects the efficacy of incorporation and the behaviour of drug release when polymer microspheres containing verapamil hydrochloride are created. The combined effects of initial drug loading, polymer concentration, external phase pH and other variables, and ANN and factorial analysis were examined as multivariate methodologies to examine the characteristics of polymer

microspheres. Compared to factorial analysis, the ANN model demonstrated more accurate and less biased predictability in addition to having better fitting capabilities [53]. Measurements were taken of the excipient ingredient quantities, drug release, and microsphere buoyancy in order to optimize alginate-based floating aspirin microspheres using ANN and Response Surface Methodology (RSM). The in vitro aspirin release pattern was better predicted by the ANN model than by the RSM model [54].

b. Solid Dispersions and Hydrogels

Solid carbamazepine dispersions have been made using poloxamer 188 and Soluplus® by ANN modelling and experimental design. Solid carbamazepine dispersions were developed to improve the drug's solubility and rate of dissolution. Solvent casting was used to make these solid carbamazepine-Soluplus®-poloxamer 188 dispersions [55]. An analysis of the relationships between various variables and the drug dissolution features has previously used ANN modelling (feed-forward backpropagation) with the logistic sigmoid activation function to optimize the medication dissolving rate. The solid medication dispersions in this investigation were prepared using poly (vinyl pyrrolidone)/polyethylene glycol combinations as carriers. The used ANNs-assisted modelling accurately predicted the solid dispersion preparations of medications with the necessary dissolving qualities and long-term physical stability [56]. Additionally, in a work by Gao and colleagues, ML was used to analyse the dissolving behaviours of solid dispersion. Using the random forest technique, a classification model was constructed to differentiate between two types of dissolution profiles: "spring-and-parachute" and "maintain super saturation." The model achieved 86% sensitivity, 85% accuracy, and 85% specificity in 5-fold cross validation. Using the RF technique, a regression model was constructed to predict the time-dependent accumulative drug release, with a mean absolute error of 7.78 in 5-fold cross-validation [57]. Han and associates discovered in 2019 that machine learning approaches might be used to forecast the physical stability of solid dispersion after three and six months. Eight learning algorithms were included to create models. The correctness of the RF model, which was 82.5%, was verified through experiments [58]. An ANN model has been used to enhance transdermal ketoprofen hydrogel. The gel's composition was optimized using the response variables' ideal values. The optimal formulation produced results that were well in line with the predictions of the ANN model [59].

c. Microparticles

A coacervation procedure was used to make benzodazole chitosan microparticles, and an ANN model was used to improve the formulation and go past the dissolution rate-limiting stage. Several optimization strategies were employed in order to attain the maximum yield, fastest dissolution rate, best encapsulation efficiency and smallest size. There was good agreement between the ANN-predicted optimum parameters and the experimental results [60].

13. Nanosystem-based Drug Delivery

a. Nanosuspension

The process of creating a methotrexate nanosuspension based on acid-base neutralization was examined computationally using the structural and electrical properties of single methotrexate molecules and molecular clusters. Quantum chemistry and molecular frontier orbital calculations are essential for reorganizing the reactivity and transport properties of molecules by identifying the acceptors or donors of their electron area. According to the computational studies, the higher interaction energies between methotrexate molecules are what drive aggregation in the cationic and zwitterionic forms of clusters and vice versa [61].

b. Dendrimers

Although there are several nanoparticle drug delivery technologies available today, dendrimeric nanovectors are the most commonly used carriers for biological and pharmaceutical applications. But it's still unclear how drugs are encapsulated in the dendrimer cavity and released from the drug dendrimer complex. The use of computational tools, such as coarse-grained simulation with quantum chemical calculations, can supplement experimental methods to determine drug-dendrimer interactions, drug encapsulation inside the dendrimer cavity, and the drug release mechanism from the drug-dendrimer complex by accounting for various properties, including the length of a simulation run, force fields, and the physicochemical properties of the drug and dendrimer [62].

c. Nanoparticles

AI assisted in the development of silicasomes, which are a blend of multifunctional mesoporous silica nanoparticles loaded with irinotecan and the tumour penetrating peptide iRGD. When iRGD enhanced silica some transcytosis, silica some uptake increased three to four times, improving overall survival and treatment outcomes [63]. In order to generate drug-carrying biodegradable nanoparticles of the triblock poly(lactase)-poly (ethylene glycol)-poly(lactase) copolymer, an artificial neural network (ANN) model has been created to determine the variables affecting the nanoparticle size. The creation of nanoparticles was modelled using a three-layer feedforward backpropagation ANN [64]. Based on the spherical central composite design, modelling and optimization were carried out to examine the effects of formulation parameters and optimize the formulation of polymer-lipid hybrid nanoparticles for controlled administration of verapamil hydrochloride. By comparing the prediction performance of ANN models and RSM, it was found that ANNs have better generalization and recognition capabilities [65]. Chitosan nanoparticles loaded with albumin were prepared using the polyelectrolyte complexation process. ANNs have been used to simultaneously determine the effects of independent factors on dependent ones [66].

d. Nano Robots

Computational technologies such as artificial intelligence (AI) maintain the fundamental components of nanorobots, which include integrated circuits, sensors, a power source, and a safe data backup. They are designed to stay out of collisions, recognize objects, locate and cling to them, and ultimately expel them from the body. Improvements in nano/microrobot technology allow them to arrive at the target location according to physiological conditions, like pH, increasing efficacy and reducing systemic adverse effects [67]. Considerations such as dose adjustment, sustained release, and regulated release must be taken into consideration while creating implantable nanorobots for the controlled delivery of medications and genes. Additionally, the release of

the drugs needs to be automated and controlled by AI tools like ANNs, fuzzy logic, and integrators [68]. AI can affect the movement and behaviour of nanorobots. To control the movement of nanorobots, a potent swarm intelligence system is required. Swarm intelligence (SI), a subfield of artificial intelligence, examines algorithms by observing how insects, birds, and mammals behave. It is still possible to collaborate without centralized control. The three main varieties of SI are particle swarm optimization (PSO), artificial bee colony (ABC), and ant colony optimization (ACO) [69]. The application of mesoporous silica nanoparticles and gold nanoparticles as nanomotors was the subject of a recent study. These nanomotors were radiolabelled for in vivo imaging. Additionally, nanomotors were quantitatively tracked using Positron Emission Tomography (PET), which improved real-time imaging and tracking of active swarming dynamics and paved the way for theranostic drug administration applications [70].

Table 1.

Top 10 Commonly used AI models in the pharmaceutical Sector

AI/Machine Learning Models	Description/Usage	References
Generative Adversarial Networks (GANs)	In order to create new chemical structures and enhance their characteristics, GANs are frequently utilized in the production of pharmaceutical products. GANs combine a generator network to create novel compounds with a discriminator network to evaluate their quality, resulting in structurally diverse and functionally optimized drug candidates.	[71]
Recurrent Neural Networks (RNNs)	RNNs are frequently used in drug development for sequence-based tasks such peptide sequence design, genetic data analysis, and protein structure prediction. They are able to document sequential dependencies and generate new sequences depending on patterns they have learned.	[72]
Convolutional Neural Networks (CNNs)	CNNs work well for image-based applications like finding possible drug targets and evaluating chemical structures. They can help with target discovery and drug design by extracting pertinent information from molecular pictures.	[73]
Long Short-Term Memory Networks (LSTMs)	One kind of RNN that is particularly good at modelling and forecasting temporal relationships is called an LSTM. Pharmacodynamics and pharmacokinetics studies to predict drug concentration-time profiles and evaluate medication efficacy.	[74]
Transformer Models	In the pharmaceutical industry, transformer models, such the well-known BERT (Bidirectional Encoder Representations from Transformers), have been used for natural language processing tasks. They are able to extract valuable information from clinical trial data, patent databases, and scientific literature, which helps researchers make well-informed judgments while developing new drugs.	[75]
Reinforcement Learning (RL)	Personalized treatment regimens and drug dosage optimization have been achieved with the use of RL approaches. In order to improve patient outcomes and aid in dose optimization, RL algorithms learn from interactions with their surroundings and make successive decisions.	[76]
Bayesian Models	In drug development, Bayesian models—like Bayesian networks and Gaussian processes—are used to quantify uncertainty and make decisions. They help researchers evaluate risks, enhance	[77,78]

AI/Machine Learning Models	Description/Usage	References
	experimental designs, and make probabilistic predictions.	
Deep Q-Networks (DQNs)	By forecasting a compound's activity and recommending high-potential candidates for more research, DQNs—a blend of deep learning and reinforcement learning—have been utilized to improve drug discovery procedures.	[79,60]
Autoencoders	In drug development, autoencoders are unsupervised learning models that are utilized for feature extraction and dimensionality reduction. They can help with compound and virtual screening by capturing key properties of compounds.	[61,62]
Graph Neural Networks (GNNs)	GNNs can be applied to drug discovery processes based on molecular structure since they are designed to handle graph-structured data. They can predict traits, model molecular graphs, and assist with virtual screening and de novo drug development..	

Other Applications of AI in Pharmaceutical Sector :

1. Poly-pharmacology

In the context of disease-related molecular networking, poly-pharmacology refers to the intentional creation of a therapeutic molecule that naturally interacts with several targets or pathways. This technique can be used to develop a therapy that is both safer and more successful than the one that is currently on the market. PubChem, CheMBL, Drug Bank, and Binding DB are a few well-known databases that provide information on biochemical pathways, binding strengths, pharmacological objectives, and physiological impacts [63,64].

2. Quality control and Quality Assurance

To effectively navigate the complex process of developing a pharmaceutical formulation within the allotted timeframe while maintaining quality, a methodical and scientifically-driven strategy is required. Information gathering include recording details regarding the drug molecules properties and excipients, and their interactions, equipment, and unit operations. First-principal models, decision trees, correlation, heuristics, and other knowledge applications are used. The manufacturing decision-making process, excipient selection, and equipment size determination are all influenced by this information and knowledge [65]. As a result, AI and its networks, tools, and technologies guarantee improved product quality, reduced waste, and higher manufacturing firm profits. The Quality-by-Design (QbD) approach guarantees that the produced goods are of higher quality. This method makes it simple to understand the important steps in the pharmaceutical manufacturing process that could affect the quality of the finished product.

3. Product development

The pharmaceutical industry is focused on improving process design for verifying an active drug, lowering production costs, and speeding up the creation of pharmaceutical products. Numerous expert systems can be useful instruments for making quick decisions in the quick creation of pharmaceuticals. The rule-based expert system, which expresses domain knowledge as a set of rules organized as IF-THEN statements, is an illustration of a decision-support tool. To tackle specific problems, these rules use input data. A rule is composed of two parts: the IF part, which makes an assumption (e.g., drug insolubility), and the THEN part, which outlines the proper course of action (e.g., using a soluble filler to address the solubility issue). This is the most fundamental form of artificial intelligence and is sometimes called a production system or an expert system. Existing rules that are provided as knowledge inputs serve as its compass. When creating tablets and capsules, these expert systems can be utilized to choose excipients. Such a system's mechanical, chemical, and physical characteristics are specified in regulations, along with the requirements for the finished product. The inference engine of the system uses this data to forecast the kind and amount of excipients needed to satisfy the requirements. After being created using this method, the product is tested to ensure it satisfies all specifications. Later, this data is sent to the system, which aids in formula optimization [66]. It is anticipated that Logica's product formulation expert system (PFES), which was developed in response to the need for quick generic formulation manufacture, will use an order of duties to direct the manufacturing process. PFES provides an approach to the development of novel formulation systems. Both the formulation object, which represents the formulation's current composition, and the specification object, which incorporates the formulation problem's current understanding, are taken into account. The formulation's development is then aided by this information. Task, control, and physical levels are the three levels at which later iterations of PFES are designed. The investigations are conducted at the control level, while the physical level obtains domain information and is reachable from the task level through a query interface. Professional and novice training, ensuring a consistent process for regulatory compliance, reducing

the time and cost of product development, and allowing experts to focus on innovation are just a few benefits of using expert systems in formulation development [67]. Integrators, differentiators, fuzzy logic, and neural networks have all been used in the development of control systems. Blood glucose levels must be regularly checked and insulin must be administered consistently in order to treat diabetes. As previously mentioned, the effective administration of insulin and regular blood glucose testing can both benefit from the usage of microchips. Combining glucose sensors, control algorithms, and mathematical models may help achieve this objective. The constraints of long-used conventional therapy approaches can be addressed by incorporating ANNs, wireless communication, and information technology into routine therapeutic practices. For example, units can receive orders from external sources via wireless connections. To manage the drug's distribution, information from these exchanges is collected and monitored [68,69].

4. Pharmaceutical manufacturing

One effective tactic for lowering lot-to-lot variations is continuous production. To reduce the variance in finished goods and patient outcomes, the FDA advises a continuous processing approach. To maintain uninterrupted production, a variety of process analytical technology (PAT) technologies are available that are both economical and effective. AI combined with PAT can help control the production process and enhance the process overall through automated machine learning [70].

5. Drug synergism and antagonism prediction

Researching the interactions between various medications is crucial when treating a patient over time. This can lower the dosage required and avoid negative side effects from taking several drugs at once. SnuGen predicts antagonism and synergism using the master regulator inference method (MARINA). It was determined that the MARINA approach could predict synergism with a 56% accuracy rate. This approach makes the "Mater Regulator" genes more understandable, which can be used to choose useful descriptors for machine learning methods. Network-based Laplacian regularized least square techniques can be used to forecast antagonistic and synergistic medication interactions. As discussed in the previous section, there are several benefits of combining different AI techniques with drug therapyA level of confidence % for correct prediction has been attained between 0.7 and 0.9, which is comparable to the most automated prediction system's performance. There is no appreciable variation in the prediction scores generated by the various machine learning techniques. Even though ANNs, Random Forest, and SVM each have benefits and drawbacks, choosing the right input parameters is the main difficulty when utilizing AI for combo therapy. When creating prediction algorithms, one must make use of the parameters that dictate the prediction model's quality [71]. Computational technologies such as artificial intelligence (AI) manage the key components of drug delivery nanorobots, which include integrated circuits, sensors, a power source, and a secure data backup [72]. They are programmed to avoid collisions, identify targets, find and interact with them, and then remove them from the body. By using physiological markers like pH, advances in nano/microrobot technology enable them to navigate to precise places within the body. This development increases their effectiveness and lowers the likelihood of systemic adverse effects [73]. Considerations including sustained release, regulated release, and dosage customisation are crucial when developing implanted nanorobots for the controlled delivery of medications and genes. Artificial Intelligence (AI) techniques including neural networks (NNs), fuzzy logic, and integrators are required for the automation of drug release [74]. Both timed release of drugs and precise localization within the body are made possible by microchip implants.

6. Nanomedicine

Pharmaceuticals and nanotechnology are used in nanomedicines to diagnose, treat, and monitor complicated diseases such as HIV, cancer, malaria, asthma, and other inflammatory conditions. The use of drug delivery systems modified by nanoparticles has grown significantly in the therapeutic and diagnostic fields because of their improved treatment efficacy [75,76]. Numerous problems in product development could be resolved by combining AI and nanotechnology [77,78]. A nano suspension of methotrexate was created using computational analysis by looking at the energy produced when drug molecules interact and keeping a careful eye out for any circumstances that can cause formulation aggregation. To assess drug-dendrimer interactions and analyse drug encapsulation within the dendrimer structure, coarse-grained simulation and chemical computation can be utilized [79]. Researchers can also investigate how surface chemistry influences the uptake of nanoparticles into cells using technologies such as LAMMPS and GROMACS. Artificial intelligence was used to facilitate the creation of silicasomes, which are a combination of multifunctional mesoporous silica nanoparticles loaded with irinotecan and the tumour-penetrating peptide iRGD. The addition of iRGD improves silica some transcytosis, which raises overall survival and improves treatment results. Consequently, silica some absorption has increased significantly by three to four times [80].

7. Predicting the mode-of-action of compounds using AI

In particular, the prospect of an AI platform that can predict the in vivo safety profiles and on- and off-target effects of drugs prior to their synthesis excites medicinal chemists. When such platforms are available, the time, expense, and attrition rates needed to develop new medications are reduced. These systems include PrOCTOR, which evaluates the likelihood of toxicity during clinical trials, and DeepTox, which forecasts the toxicity of novel medications [81,82]. If a comprehensive and reliable dataset containing information on the toxicity and therapeutic qualities of a wide range of pharmaceuticals becomes available, the industry can boost the predictive accuracy of these platforms by sharing and exchanging data. Recently, a new AI tool called SPiDER was developed [83] to support natural products for drug development in place of chemo-proteomics. Lapachone, a naturally occurring naphthoquinone with encouraging antitumor effects that is presently undergoing clinical development, had its molecular target predicted using SPiDER as a proof-of-concept. The platform anticipated that lapachone would modulate 5-lipoxygenase (5-LO) allosterically and reversibly. The prediction is confirmed using a 5-LO functional test. Read-across structure-activity relationships (RASAR), a different AI technique, has proven to be successful in predicting the toxicity of unknown substances. RASAR is useful in this prediction process since it makes use of a large chemical library and connects molecular structures to dangerous characteristics. [84]

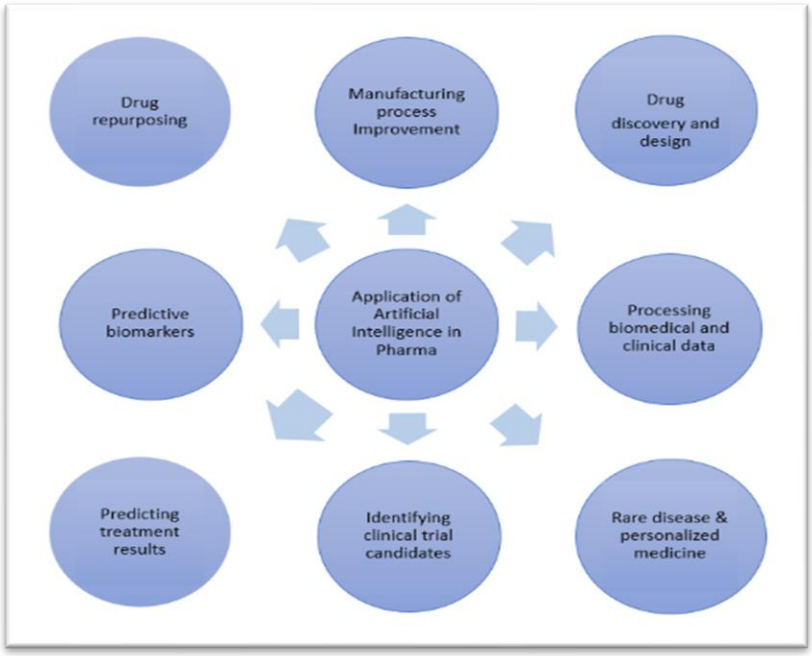

Fig. 2 Application of artificial intelligence in pharma

Conclusion :

AI has a bright future in the pharmaceutical sector, with the ability to completely transform PMS, industry management, regulatory affairs, drug discovery, and pharmaceutical product development. Large volumes of biological data can be analysed by AI algorithms to find possible therapeutic targets and speed up the drug discovery process. Clinical trials can be conducted more effectively and economically by using AI-driven simulations in drug development to forecast how chemicals will interact with biological systems. AI-powered solutions can also improve supply chain management, increase regulatory compliance, and expedite the manufacturing and formulation development processes. Large databases of data and information are essential for AI algorithm creation and training. In the past five years, more than a thousand reviews and research publications about the use of AI in pharmaceutical applications have been published. This demonstrates the importance of improving and expediting the procedures and processes used in present research. However, in the end, the most effective AI-driven technologies and applications for real-world use or commercialization will be determined. The incorporation of artificial intelligence (AI) into the pharmaceutical sector will undoubtedly spur innovation, enhance patient outcomes, and change the face of healthcare as technology develops.

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