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EMBEDDING ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN PHARMACEUTICAL SCIENCE AND FORMULATION DEVELOPMENT

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ABSTRACT:

Background:Artificial Intelligence (AI) and Machine Learning (ML) have wildly succeeded in pharmaceutical science and formulation development.
Main body:AI is nothing but a combination of science and engineering with computational understanding to construct intelligent machines and brilliant computer programs, and ML is a branch of AI where computers are made to improve their performance through experience. There are various other branches of machine learning, such as Artificial Neural Networks (ANNs), Fuzzy logic, Neuro-fuzzy logic, Evolutionary computers, and Genetic algorithms.
Short Conclusion:AI has already gained access to pharmaceutical science and formulation development and also greatly benefited the fields by its use, there isstill unpredictability about how AI is going to shape the future of the work field, and there are some concerns regarding how it can replace humans in various fields. This review summarizes all the aspects of AI & ML from history, goal, principle, branches, use in formulation development, applications, and their future.

Keywords: **-** Artificial Intelligence (AI), Machine Learning (ML), Artificial Neural Networks (ANNs), Fuzzy logic, Neurofuzzy logic, Evolutionary computer, Genetic algorithms.

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1. BACKGROUND:

Artificial intelligence can be defined as the branch of science and engineering with the computational understanding capable of analyzing complex medical data[1].Artificial intelligence, also known as AI, is the core of the fourth revolution of science and technology, providing facilities to achieve precision public health and personalized medicine. The research has achieved and acknowledged the development and promotion of intelligent healthcare systems worldwide along with some excellent medical advancements[2-6].

It alsogenerates opportunities for all-around medical service promotion, including fast data processing, accurate image interpretation, workflow improvement and reducing errors in the healthcare system practice[7].The father of artificial intelligence, John McCarthy, defined artificial intelligence as "The science and engineering of making intelligent medicine, especially intelligent computer programs". Artificial intelligence is a way to make computer programs and software think intelligently like an intelligent human being[8].

Along with various benefits, there are some concerns and controversies as artificial intelligence medical services increase accessibility to thegeneral public. Some populations cannot accept artificial intelligence because of its drawbacks, such as:-

1. Disease diagnosis and treatment inaccuracy.
2. Medical students and doctors stress that they might get replaced by the presence of artificial intelligence.
3. Also, artificial intelligence can reduce the patient-doctor relationship[9-12].

As the public can have different opinions and anticipation towards the rapid artificial intelligence development, an extensive survey is carried out to gather the public's opinion for understanding their viewpoints and demands by their comments[1, 13-15].The survey can help understand the deficienciespresent in the current implementation of programs and provide guidance for the further development of artificial intelligence[16].

Artificial intelligence (AI) now plays an essential role in day-to-day life. There have been advancements in numerous different fields, such as:-

1. Recognition of image and speech.
2. Processing of natural language and many more[17-19].

It is considered a demonstration of intelligence by the machine. This term is basically used in the machine to show cognitive (similar) behavioursassociated with the humans, such as learning, problem-solving etc.[20]. It is commonly based onhow the human brain actually thinks and how humans can learn, decide and work to solve any problem and use those outcomes to develop intelligent computer software and systems[8].

2. MAIN TEXT: There are various branches of AI; among all of them, machine learning is considered the most recent used technology of AI in the pharmaceutical field. Natural language processing(NLP), Robotics, and Expert systems are some other AI branches becoming highly popular in the healthcare field, such as diagnosing any disease, monitoring patient's health, and other robotics surgery. However, these branches are yet to receive attention compared to machine learning in the pharmaceutical science field [21, 22].

2.1 Machine Learning (ML)

Machine learning is considered a subdivision of artificial intelligence that helps the computer to learn from data. ML is a comprehensive term used for several different methods to achieve AI[23] and is considered the main driving force in developing AI applications[24]. ML is a vital AI tool to obtain a deep understanding of data, prediction making and providing decisions by computer with the help of ML[25]; computers can make conclusions by their own rules using advanced software processes[26].

Many of the processesused in machine learning were already earlier used bystatisticians. The generation of a large amount of recent digital data in the form of image, transactions, texts, human and environmental sensing data which are considered "big data", can be stored in the cloud rather than on the premises, which make their analysis faster and cheaper by using graphical processing units, which train the machine to

perform a task without being utterly dependent on a program to do it[25].Internet searches, good and services recommender systems, e-commerce, image and speech recognition, identification of images, sensor technologies and robotics devices are various machine learning methods[27].

2.2 Goals of Artificial Intelligence

1. To create an expert computer program on the system:- The system created should have excellent behaviourand should be able to learn, demonstrate, explain and give advice to its users.
2. To implement the intelligence of humans in the machine:- The system created should be understood, learned, taught and behave just like humans[8].

2.3 History/Origin of Artificial Intelligence

YEAR	INNOVATION
1923	"Roosum's Universal Robots"(RVR) was a science-fiction play by Karel Capek. The play had its world premiere in London, and the word "robot" was first introduced in that play.
1943	Neural network formulation was first laid.
1945	The term "robotics" was coined by Iraac Asimov
1950	For the evaluation of computing machinery and its intelligence, a test called the "Turing test" was introduced by Alan Turing.
1956	The term "Artificial Intelligence" was coined by John McCarthy. At Carnegie Mellon University, the first AI-based program was demonstrated.
1958	John McCarthy developed an artificial intelligence programming language called "LISP",which was designed to manipulate data.
1964	At MIT, Danny Bobrow's showed that computers could easily solve algebra word problems because they can understand computer language.
1965	For solving the interactive problems in a dialogue in English, a natural language processing computer program called ELIZA was created at MIT by Joseph Weizerbaum.
1969	The scientists at Standard Research Institute developed a robot "Shakey" equipped with perception, locomotion, and problem-solving capability.
1973	A Scottish "Freddy" with the capability of using vision to locate and assemble models was developed by an assembly robotics group at Edinburgh University.
1979	Stanfort Cart, the first computer-controlled vehicle, was built.
1990	Many significant advancements were made in AI:- • Demonstration in ML • Scheduling • Natural language understanding • Case-base reasoning • Vision, Virtual reality • Gaming
1997	A chess-playing supercomputer called "Deep Blue" was developed by IBM. It won a game against the world's chess champion, Garry kasparov.
2000	A robot, "Kismet", was displayed by MIT, who had a face to express different emotions. Another robot, "Nomad", developed by the Robotics Institute, was developed to demonstrate a robot capable of travelling long distances, so it explored Antarctica. Many interactive pet robots were available commercially.

AI is an advancing field of science.The scientific disciplines that underlie AI include computer science, biology, mathematics, statistics, cognitive psychology, decision theory, neuroscience, linguistics, cybernetics, and engineering[28]. The inventor of the first mechanical computer Charles Babbage the 1850s, to Alan Turing, the father of the general-purpose programmable computer, was the first to ask the question, "can machines think like humans?" 1950s[29]. Computer scientists and science fiction writers' imaginations were captured by the idea of machine intelligence equivalent to the human brain[30,31].

Artificial Intelligence was first used in the summer workshop in New Hampshire at Dartmouth College. The workshop was based on "the artificial intelligence problem" as one "of making a machine behave in ways that would be called intelligent if a human was so behaving"[32]. In simple words, Artificial intelligence may easily be understood as a general term that focuses on using computational methods to replicate human intelligence.

Alan Turing, in the 1950s, proposed an operational test for measuring machine intelligence. The test was called the "Turing test", which measures the ability of a machine capable of human-like intelligence or indistinguishable from a human[26]. For a computer to qualify for the test, the human interrogator should not be able to tell whether the written questions posted came from a machine or a human[29].In 1956, a workshop, "Dartmouth workshop", was held whose aim was to develop a branch of artificial intelligence that could pass the Turing test, which indicates the development of a level of intelligent machines that exceeds or matches the intelligence of humans[26].

To qualify, some requirements must be metfor the Turing test-

1. Natural language processing:- A computer should be able to understand speech.
2. Knowledge representation:- A computer should memorize what it knows or hears.
3. Automated reasoning:- A computer should be able to keep records to answer various new questions and draw a conclusion from them.
4. It should be adaptable to any changing circumstances [28].

The other two fundamental requirements are:-

5. The vision of a computer
6. Physical interaction

After fulfilling all these requirements, a computer would satisfy a test called the total Turing test[33-34]. These six requirements now play an essential role in artificial intelligence research and development[28].

Competitions for machines are generally divided into the categories:-

1. Strong AI (Actual thinking) or Artificial General Intelligence(AGI)
2. Narrow or weak AI (Simulated thinking)[28]

It is said that AGI is many decades away, but there are some future predictions that there will be an "intelligence explosion" once a machine can achieve AGI[35].

The category of artificial intelligence that is currently used today is narrow or weak AI. It uses physical devices such as sensors, robots and digital software to deliver comprehensive AI services[36].

2.4Principle of Artificial Intelligence

Despite its long history, Artificial intelligence still does not have a standard definition. However, using computer systems for human intelligence mimicry is the basic concept behind AI. Warren McCulloch and Walter Pitts, in 1943, got inspired by the physiology and function of neurons in the brain and proposed a computational model of artificial neurons[37]. The artificial neurons work the same as human neurons by being "on" and "off" in response to neighbouring neurons sufficient stimulation[38]. In recent years, AI has gained advanced increasing interest in a wide range of fields such as healthcare[39], transportation[40], engineering[41] etc.

Machine learning(ML) is commonly considered a branch of AI where computers are made to modify their actions, such as making predictions. ML process can be classified into two:-

1. Supervised machine learning:- The process uses generalization to respond to training

example sets. Basically, training examples are provided in the dataset as input-output data. The output is called the correct response or answer and is termedthe target. So, the basic goal of supervised machine learning is to predict outcome data closer to the target. For example,

- Support Vector Machine (SVMs)
- Random Forests (RF)
- Artificial Neural Networks (ANNs)[42]

2. Unsupervised machine learning:- Unlike supervised learning, no input data or training examples are provided in the case of unsupervised learning. For example,
   - Principal component analysis (PCA)[42]

Nevertheless, some supervised models can support unsupervised models, such as SVMs and ANNs[43].

2.5Different Branches of Artificial Intelligence

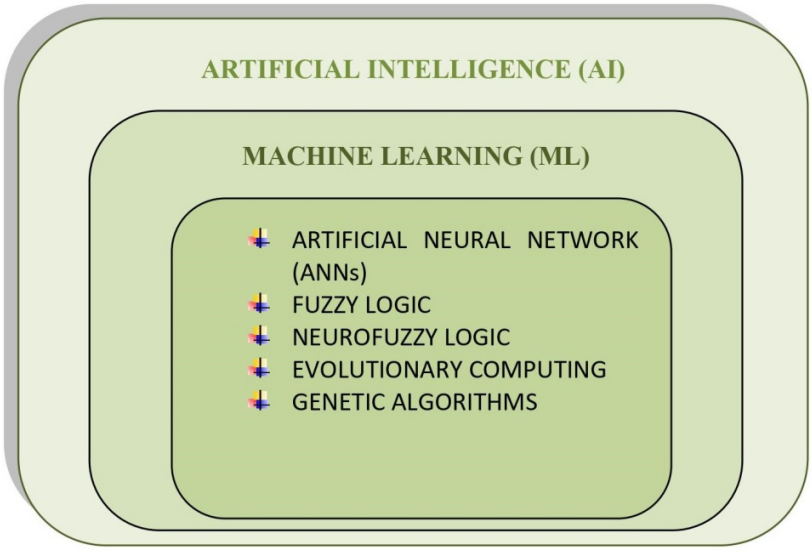

FIGURE 1:- This schematic diagram represents correlation in between the Artificial Intelligence (AI), Machine Learning (ML) and Artificial Neural Networks (ANNs).

***2.5.1 Artificial Neural Networks (ANNs)*:-** They are biologically inspired models that mimic the ability of the brain to learn. A billion of processing units called neurons are present in the brain. All these neurons are interconnected with the help of a number of synapses[44]. A human neuron consists of a nucleus and cells that control activities. Dendrites,thread-like structures around neurons, can carry the information action to the cell and axons just like a long thread that carries information to the next cell[44].

Inspired by the human neuron, ANNs also consist of artificial neurons or processing elements that can learn from the input data. The main component of the neural network is the neuron, which is considered a mathematical processing unit where one or more input data are given to produce an output. For a neuron, every input data given has a well defined relative importance, and the neurons calculate all the independent outputs to calculate the final output[45].The output data are created and then modified by activation function or transformation

function before being transferred to another neuron. The processing unit is called perception, a feed-forward system by which the data are transferredfrom input to output in the forward direction[45].

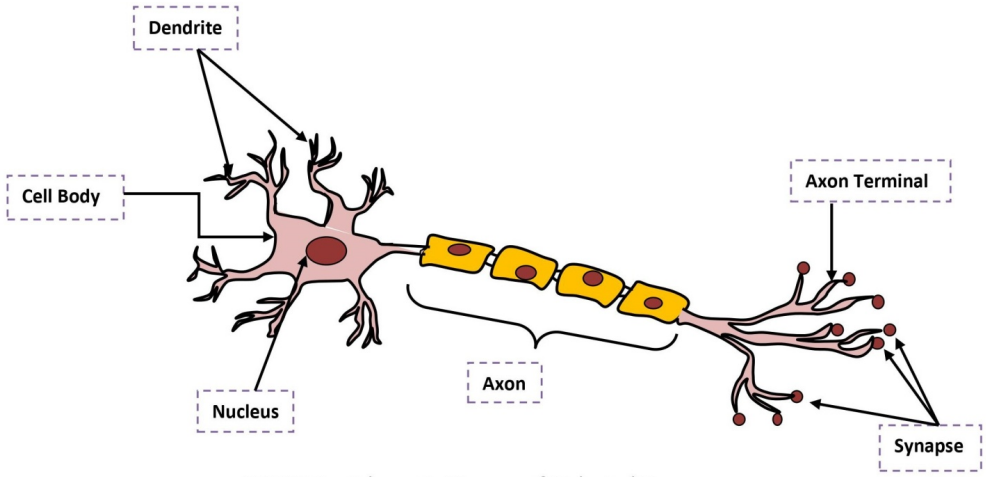

FIGURE 2: - Schematic Diagram of Biological Neuron.

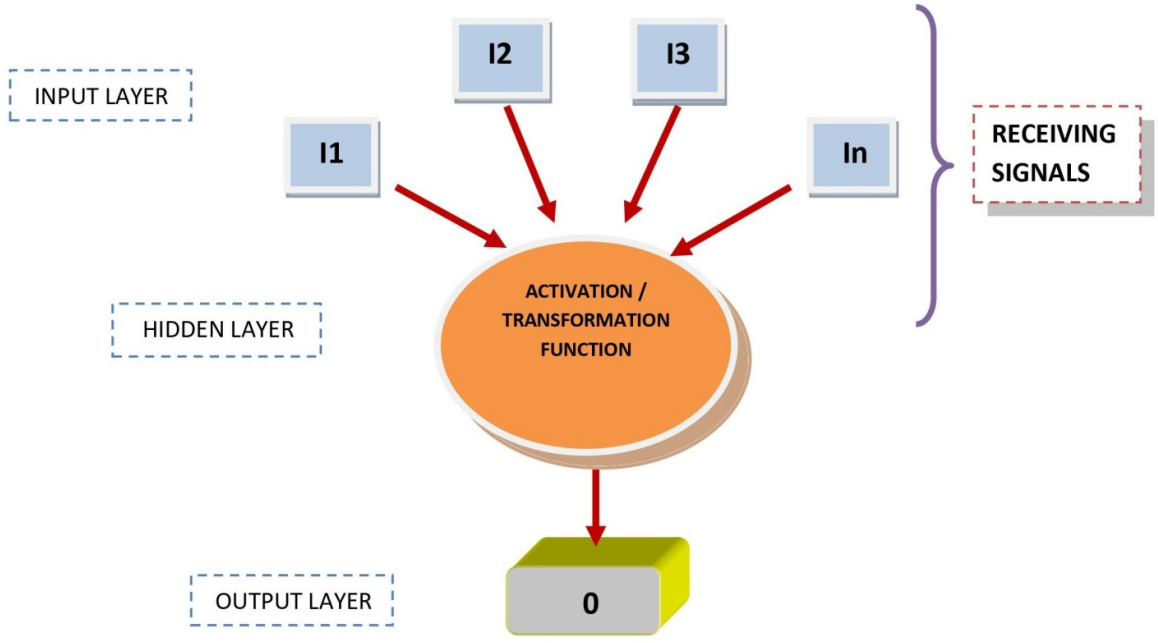

FIGURE 3:- Schematic diagrams of Artificial Neural Networks (ANNs).

ANNs have three main components:-

i. Input layer:- It corresponds with dendrites in the human neurons to transfer information to the second layer[37].

ii. Hidden layer:- Now, this layer is sandwiched between the two-layer input and output layer, so it is called the hidden layer. The fundamental role of this layer is to create a connection between the input and output

layers. There isa number of neurons present in this layer. So the number of neurons to be used depend on the trial and error method because using a definite number of neurons can cause a reduction in ANNs learning ability, whereas using too many neurons can result in memorization of training data,thereby decreasing the generalization ability of the ANNs[46]. Thus, the number of neurons capable of giving the highest correlation coefficient and the lowest error should be selected.

iii. The output layer is the final layer of an artificial neuron that consists of output targets[37].

The process of making an artificial neuron is called learning or training. The input data are received in the input layer, which is carried on to the next layer called the hidden layer, where several activation functions are carried out, such as logistic, identity and exponential function and finally, in the last layer,i.e. output, the output is calculated[48,49].

2.5.2. Fuzzy Logic:- In fuzzy logic, the judgment or a proposition is either true or false. So the map of the hypothesis lies either in the "true" side or entirely outside it that is "false". If the hypothesis result is 1 then the hypothesis is considered true, and if the hypothesis results in 0 then the hypothesis is considered false. For example, if 20ºC room temperature is considered as "comfortable", then temperatures outside this range that are 19ºC or 21ºC are considered "uncomfortable"[45].

Lotfi Zadeh, in the 1960s, introduced the concept of fuzzy set[47]. Unlike fuzzy logic, the membership functions are not confined between 0 and 1, but any continuous values between these two limits can be taken. For example, four rules govern the working of a fan heater which are-

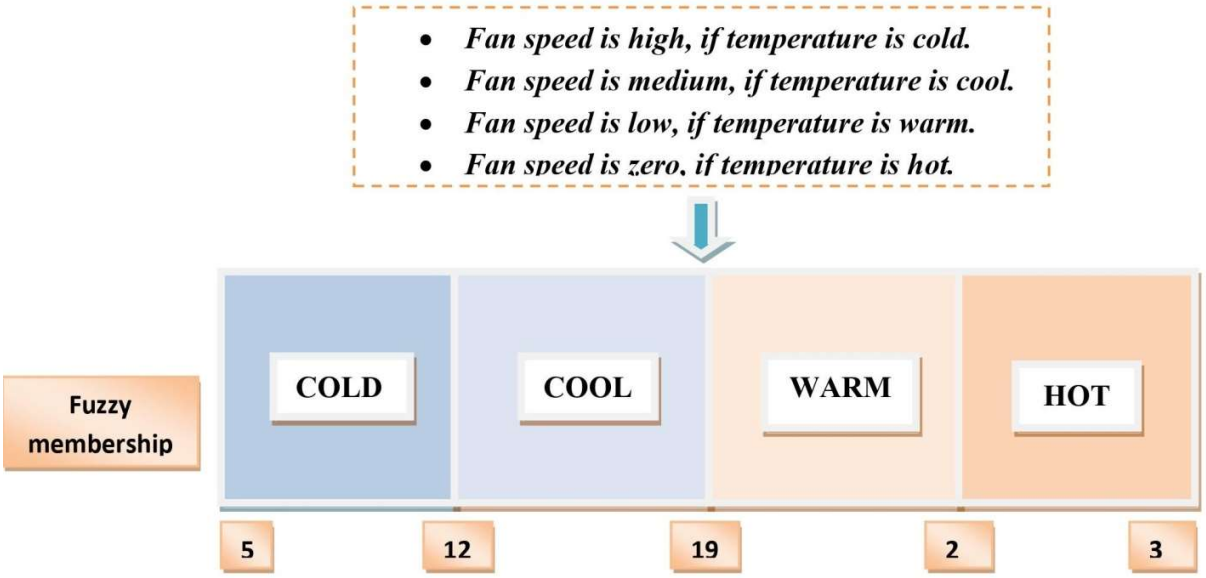

FIGURE 4:- Schematic Diagram of example of Fuzzy Logic

For a better understanding of the fuzzy logic concept, let us take an example of the tablet disintegration test. The formulator is looking for the disintegration time of 300s. So any value that is less than 300s can have a desirability of 1 (i.e. 100%), but if the disintegration time is 310s, it is not considered entirely undesirable, and the desirability value can be 0.9[45].

2.5.3. Neuro-fuzzy Logic:-

Recently, various efforts have been made to merge two different technologies to create new methodologies. Neuro-fuzzy logic is an example of merging technologies that combine the capabilities of neural networks to learn from the data with the concept of fuzzy logic to convey complex conceptseffortlessly.

The lead of this technology is that it can extract the information from the data and represent it in an effortless manner that is very easy to understand.The neuro-fuzzy logic is architectured with two extra layers,i.e. for fuzzification of inputs and defuzzification of outputs[45].

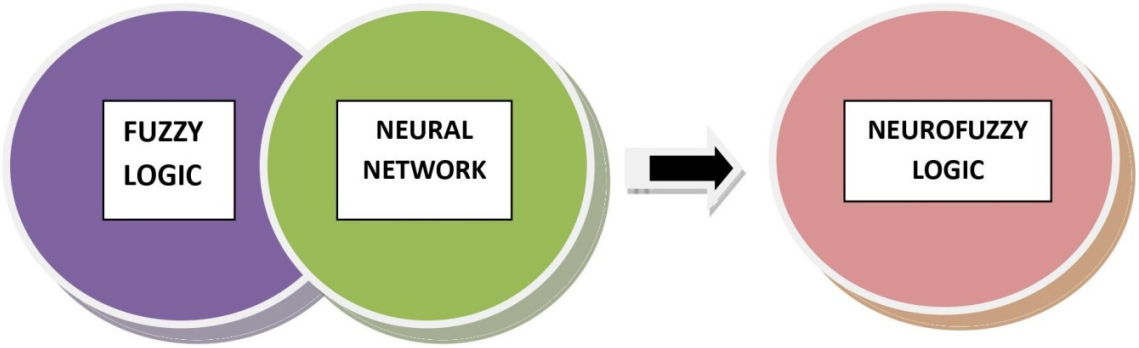

FIGURE 5: - Schematic Diagram of Neurofuzzy Logic

***2.5.4. Evolutionary Computing*:-** It is considered the study of computational systemswhere this technique uses plans from natural evolution, and biological systems also get developed and inspired by them[45].

***2.5.5. Genetic Algorithms*:-** Inthe 1970s, John Holland introduced a genetic algorithm[48]. A searching technique is provided, which is used for optimization, and it is considered a very tedious process. For performing this technique, initially, a population of solution is created, and every member of the population is checked for fitness. The fittest of all the solutions is considered the "parent" for the next generation. Through the process of recombination and mutation, further degree of newness is introduced into the population so that genetic algorithms can find the ideal global solution. The genetic algorithm is based on the concept that the different criteria of "fitness" can be described for the population[45].

Koza, in the 1990s, defined genetic programming as a subset of genetic algorithms. Currently, it only has some limited use in the pharmaceutical formulation development, but it is considered that in the near future, its use will increase as it shows similarity with the neural networks and also has transparency related to the mathematical expression[49].

Along with many advantages of this technique, there are some disadvantages, such as:-

- This technique is considered time-consuming.
- In the formulation, its applications are less understood[45].

3.ARTIFICIAL INTELLIGENCE IN FORMULATION DEVELOPMENT

For the last 15 years, all artificial intelligence technology branches have been widely used to design and optimize the formulation[45].

The development of viable drug formulation with desired qualities involves blending inert products and additives with the active pharmaceutical ingredient (API) to formulate viable drug products with desired characteristics[50]. Recently, optimization technique

has been incorporated in the development of optimized drug formulation, which is improved in the following things:-

- Improved efficacy.
- Long-acting therapeutic effect.
- Side effects reduction.
- Increased stabilization and shelf-life of Active Pharmaceutical Ingredient (API).
- Increased patient compliance[50].

Depending on which route of administration is desired, the APIs are formulated first by using various materials such as inert additives like lipids, surfactants, polymers, and other APIs, if any. They can be made in various delivery systems such as Microparticles(MP), Nanoparticles(NP), Multicomponent systems etc. [51-54]. Finally, they are formulated into desired final products, for example, solid, liquid or parenteral formulation[50].New innovative drug delivery processes and economic development processes are required to bring new effective medicines to the market[55].

The main drawback during the formulation development was the incapability to forecast how different compositions or the combination of the APIs and the other substances influenced the performance of the formulation. So to overcome this drawback, pharmaceutical scientists have taken on the computational modelling approach[55]. For example,

- Molecular docking studies[56].
- Cheminformatics tools[57].
- Molecular dynamics simulations[58].

Molecular learning is a subdivision of AI whose main aim is to train the computational model based on the data. For example, for knowing the stability of a particular drug formulation, machine learning can be helpful as it can consider data from the earlier experiments where the API formulations' stabilitywas examined. There have been some recent developments in machine learning algorithms, such as,

- Broad availability of faster computer hardware.
- Development of user-friendly ML toolkits.
- Improved availability to powerful ML models[55].

With such developments in this field, there has been an explosion in the ML and AI application, which thereafter has led to further applications such as:-

- Enhanced cancer diagnosis[59-61].
- New antifibrotics discovery[62].
- Development of new antibiotics molecules[63].
- Also, the development of self-driving laboratories[64, 65].
- Development of new algorithms to forecast the chemical reaction of the products[66].
- Optimization of chemical reactions by deep reinforcement learning[67].
- Determining the third-dimensional protein structure from the amino acid sequence by using deep reinforcement learning[68].

Current inventions for the development of new drug products and the procedure for their optimisation pose similar challenges to others that have already been examined by machine learning. Some of the disadvantages in the current drug formulation development are expensive, laborious and time-consuming to achieve a required formulation with properties such as increased solubility of API by selecting appropriate materials. By using the power of AI and ML, pharmaceutical scientists can develop such formulations using the data stored or by optimal experimental planning[55].

ML models are generally advanced just to overcome all the challenges faced by pharmaceutical scientists, including:-

- ✓ Predicting the effect of the additives used in the APIs solubility.
- ✓ For determining protein's chemical and colloidal stability.
- ✓ API formulation physical stability prediction.
- ✓ For determining API loading capacity and its release rate from the advanced delivery system. For example, microparticles and nanoparticles[55].

4.APPLICATION OF ARTIFICIAL INTELLIGENCE

Starting from the beginning and ending at the endof pharmaceutical product development, artificial intelligence branches such as machine learning have been used. There are various sections of pharmaceutical drug development where ANNs, in combination with various machine learning techniques,can be used[37].

i. **Artificial intelligence in drug design and development:-** Machine learning can be significantly used in the pharmaceutical sciences to discover a drug for usefulness in high-throughput screening, computer-aided drug design (CADD) and combinational chemistry[69-70]. The quantitative structure-activity relationship (QSAR) is the earliest area in which artificial intelligence was applied[71-73]. Compound physiochemicalproperties and chemical or biological activities correlate with the QSAR approach[74, 75]. Molecular weight, hydrogen bonding capacity and partition coefficient(logP) are some of the commonly utilized physiochemical properties for QSAR studies. Hence, due to its functionality and achievement, the importance of artificial intelligence continues to grow in pharmaceutical product development[76].

ii. **Artificial intelligence in pharmaceutical preformulation:-** Preformulation is defined as a process in which physicochemical properties of the compounds used for manufacturing drug products are assessed. Physicochemical property determination of the drug compound plays a critical role in providing the idea about products solubility profile, interaction with the excipients used, the bioavailability of the compound, stability and various other parameters[77].

The first step in the preformulation study is the determination of the aqueous solubility of the drug compound. The drug to be absorbed should own a significant degree of solubility in water. It is ubiquitousto manufacture oral, opthalamic, topical, parenteral and various additional routes of administration. If a compound does not have acceptable solubility profiles, then various other techniques can be used to upgrade the solubility of the particular compound, such as complexation technique, surfactant usage, salt formation, and co-crystals formation, using hydrotropes etc. [78-80].

For example, various computational approaches, machine learning techniques[78], and molecular dynamics simulation[81] can be used *in silico* forecasting drug substance aqueous solubility.

iii. **Artificial intelligence in pharmaceutical formulation development:-** The most crucial process in drug development is the formulation of drug substances and compounds into the final drug product used for administration by the patients. The most crucial machine learning branch in predicting the pharmaceutical formulation is ANNs which have gained great interest in this field [82]. Various number of studies have already utilized ANNs in the development and optimization of the manufactured formulation and the factors related to parameters of formulation, for example, drug release and drug dissolution. The optimization process for the formulation includes the compounds used and the operating condition by utilizing the machine learning process. Specially ANNs haveprovided great success and exhibited their promise for further application in the future[37].

5. FUTURE OF ARTIFICIAL INTELLIGENCE

Now that artificial intelligence has gained access to the pharmaceutical science field, it will be tough to restrict its growth. The conclusion of adopting this new technology is to embrace the new realities developed based on the present situation, which can create immense pressure on the late technologies that are already in the market for so long and can lead to their falling out of the race. Soto prevent the technologies from lagging, there is a need for them to adopt the recently made approaches and become powerful. AI is recently a booming technology that promises a complete transformation in the functioning of science, society and the business field[26].

Artificial intelligence and machine learning can significantly benefit the pharmaceutical industry's development. AI can be used for any aspect of drug manufacturing, starting from evaluating raw materials to their marketing. The last 10 years have seen a significant increase inthe number of pharmaceutical companies and business stamps using AI computational technology for pharmaceutical product development. AI can be very useful in improving decision making and for the development of new and successful medicines. AI technology has yet not created that control on the pharmaceutical industry because of several challenges such as a large amount of data management, prescribing solutions for various problems, lacking skillsets, not many investments in this zone etc. and other essential factors for not using AI are lack of staff, safety, regulation, budget etc. There is still an unpredictability about how AI will shape the coming future of work, and along with this, there are concerns regarding how AI can replace humans in different fields in the near future[83].In recent times there are various AI-enabled computational applications that are entering the workspace that need attention from occupational safety and health practitioners, workers, employees, researchers etc. before introducing any AI-enabled computational program devices in the workspace, there is a need for pre-placement safety insurance and health view, as well as all of the benefits and risks caused by that programs,should be well known to avoid it. The overall approach to AI and its implementation in the future works needs an occupational safety approach and development of strategic planning for better anticipation and preparation if any AI-enabled technological challenges are possible or the safety of works, well-being and health are hampered[37].

6.CONCLUSIONS

Artificial intelligence leads to the digitalization of the pharmaceutical workspace, where numerous technologies and software of AI and ML are used. There is a more significant potential for the development beyond the traditional AI application with the growth in the success of machine learning technology in various pharmaceutical workshops. Depending on the types of data entered and dataset size, suitable machine learning technology can be chosen. So, the machine learning method to be chosen is generally a task-specific process. Using an advanced AI algorithm to build a robust application with the help of sufficient curated data may someday become a prevalent practice to solve the challenges in the pharmaceutical drug development process. With the fast, efficient and economical solution, it can be predicted that AI will definitely flourish in an era of digital pharmaceutical science[37].

In the coming near future, there is a higher possibility for the development of various small scale software and biotech companies that will be strengthening the artificial intelligence technology by exploring new ways for the drug formulation discovery and also development process. Not all the companies will be successful in this work, while numerous will cease to function by failing in their ambition or may run out of investments. At the same time, the rest can achieve enough success to keep themselves sustainable in the market. Only some will achieve the highest success if AI continues to be helpful in drug discovery and formulation development which is expected to be the case. Then AI can be progressively incorporated into the workspace of both the large and small scale software and biotech companies. How academic science is performed recently will be changed entirely by the patterns and connections in between the data that can be discovered in large numbers automatically.

Moreover, with the developmentof AI technology, it indeed becomes imperative to think of its impact on the employment process; many of the jobs will be altered entirely, some will definitely disappear, but also some new roles in the research and management field will be created that will require researchers and managers. Indeed a diverse change in the field can be assumed in the coming 20 years to increase the efficiency and capacity of the industry to encounter the unique needs of the patients. Nonetheless, with several developments, there comes some fear of potential data exploitation, equilibrium between human and AI control and also the effect of the technology on employment as well as the employees in the working organization[83].

List of Abbreviation:

AI : Artificial Intelligence

ML: Machine Learning
ANNs: Artificial Neural Networks
NLP: Natural language processing
AGI : Artificial General Intelligence
SVM :Support Vector Machine
PCA : Principal component analysis
RF: Random Forests
CADD: Computer-Aided Drug Design
QSAR : Quantitative structure-activity relationship

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