



Recent advances in computer-aided pharmaceutical formulation and cost-effective manufacturing approaches

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ABSTRACT

Computer-aided pharmaceutical formulation represents a major change in drug development by using advanced computational tools to optimize formulation and manufacturing processes. These components integrated with experimental design methodologies (factorial and response surface methodologies) allow for the rapid evaluation of a number of variables, which facilitates the evaluation of an entire experimental system, eliminating a substantial number of experimental trials, lowering times and costs compared to traditional experimental practices. In addition, *in silico* modeling supports and facilitates early-stage development by enabling virtual predictions of compatibility/stability, which eliminates or minimizes laboratory work, while improving quality assurance. In general, computer-aided formulation promotes reproducibility, innovation, and provides robust validation for design and process.

1. INTRODUCTION

With the increasing use and improvements in the existing technology, integration of the information technology field and the pharmaceutical field can be considered as one of the greatest and important achievements in the history of the field of pharmacy. The use of technology is usually considered an advancement, as its use brings automation to the ongoing processes. Even though it is not very easy to bring this system into application in reality, the efforts taken over it will definitely bring ease in carrying out the related activities. In the near future, the impact of technology in this field can be seen reaching so far that the training of information technology will probably be included in the curricular activities of academic [1]. Coming

to the pharmaceutical industry, one of its main objectives is to develop a quality product.

While formulating a dosage form for a particular drug, many of the optimization trials are supposed to be conducted before finalizing a single best formula and process [2]. The optimization principles can be placed simply, as the process of finding the best possible solution in the presence of constraints, rather than formulating the best formulation ever. Earlier, the process of optimization was carried out using a trial-and-error method or a “changing a single parameter at a time” approach to determine its exact effect on the process as well as the formula. However, this approach was found to be very time-consuming and resource-intensive. The implementation of computer-aided design of dosage forms later surmounted many of the drawbacks of the earlier method. The computer programs help in reducing the number of experiments to be carried out. This is achieved either by filtering and narrowing down the number of experiments/parameters or by imitating them to get the generalized idea about the mechanisms or the basic understanding of the experiments [3]. This review highlights a

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few such advances in the use of technology in the formulation and development of dosage forms. Three techniques described here are 3D printing, artificial intelligence (AI), and computer simulations. These technologies are commonly used and also present a very promising future in the field of pharmacy.

Quality by design (QbD) systematizes the pharmaceutical formulation process using AI, including deep learning and machine learning algorithms, to extract useful patterns from large experimental and manufacturing datasets. These AI-driven tools, along with model-informed drug development, predict relevant material properties, identify the best acceptable formulation, and mitigate risk. Moreover, deep learning performs well at modeling complex or nonlinear relationships among formulation variables and product performance, which helps reduce trial-and-error approaches to formulation and leads to better data-driven decisions in formulation design. Using AI and deep learning in QbD delivers development speed and lower costs while increasing the chance of consistent high-quality pharmaceutical products by associating formulation attributes and process conditions with a desired therapeutic performance [4–6].

Some of the free tools and paid tools/software used in formulations and development are given here. Free tools are: a) FormulationAI: A complete AI-based web-based platform for the design of *in silico* drug formulations across six drug delivery methods (with predictive models). b) GROMACS: Open source molecular dynamics simulation software for visualizing drug-excipient interactions and conducting molecular simulations in formulation science. c) Click2Drug: Listing of various free computer-aided drug design tools, including formulation tools. Paid Software/Tools are: a) F-CAD Cloud: A web-based platform based on computing via a GPU for *in silico* design related to solid dosage form and pharmaceutical formulation design to decrease the experimental burden. b) Dotmatics Formula Development Software: Supports research decision-making and workflow management in the development of formulation for premium product design. c) Formula Bot: The AI data analyst/insight transformation tool turns your experimental data into insight for formulation design (offers a free/trial and paid plans) [7].

The combination of digital twins with machine learning-based process control in pharmaceutical manufacturing is a transformative development, whereby a digital twin (virtual representation) continuously updates the digital representation of the manufacturing process using real-time data, and simulates, monitors, and optimizes the pharmaceutical manufacturing operations. The integration of machine learning algorithms helps improve overall efficiency, decrease downtime, and ensure consistent product quality. It also enables near real-time operations, predictive maintenance, and adjustments to multiple process parameters. The technology can proactively identify possible failures, optimize input and resource utilization, and assure compliance with regulatory requirements by tracking comprehensive data and operational characteristics. Most importantly, the integration of machine learning and digital twins will accelerate time-to-market for the pharmaceutical production process while lowering cost and waste [8].

The paper demonstrates how AI-using applications such as DeepChem and GraphConv have offered guidance in the curation of nanoparticle composition for sustained release. In one case, genetic algorithms and ANN-based models were used to optimize polymer blends and release rates for hydrogel and oral solid formulations. Machine learning based tools have been utilized for in-the-moment characterization, support for decision-making, and excipient selection for personalized oral therapies that have a greater probability of success for targeted delivery of medications of medicines, and in cancer therapeutics [9].

Investigation on a global computer-enabled drug formulation platform, such as FormulationMM, illustrated strong modeling experimentation with large excipient databases and algorithmic predictive protocols. Platform(s) utilizing physiologically based absorption modeling and molecular dynamics simulation shortened development cycles for oral and injectable dosage forms through rapid virtual screening and compatibility testing to support and validate clinical translation studies [10].

Optimization of the controlled-release verapamil hydrochloride nanoparticle formulation using artificial neural networks combined with genetic algorithms and response surface methodology (RSM). This research demonstrated that AI facilitated drug release prediction and enhanced formulation efficiency [11]. AI-enabled 3D printing of pharmaceuticals for a drug product where AI models estimated the rhodium polymer properties, the processing temperature, and the drug release kinetics, allowing for tailored personalized dosage forms [12]. The revolutionary potential of AlphaFold and *In silico* Medicine's platforms that utilize AI to dramatically reduce the time needed for drug development through accurate prediction of protein structure and also the design of new drug candidates, including for the therapy of idiopathic pulmonary fibrosis [13].

Patient-centric drug formulation platforms enable the development of relevant drug products by providing rapid, low-cost, and precise formulation design capabilities. Tools exist that range in their application, with some predicting the physicochemical properties of drug compounds, others optimizing drug release profiles, and some relatively new tools simulating the drug product manufacturing process. The scalability of these platforms also differs, with some only being able to calculate experimental formulations on a small scale and others being able to predict an entire batch in an industrial setting. Furthermore, several tools are becoming more regulatory-ready through validated models and documentation, but the regulatory acceptance of these tools is still an issue in many situations, based on the region and use of the tool, requiring further experimental data to validate the predictions. Therefore, the tools complement the traditional formulation design approaches by decreasing the time for formulation iterations, lowering experiment costs, and enabling reproducibility, but differ in their applications and ability for integration into a manufacturing and regulatory process [14].

Both the FDA and European Medicines Agency (EMA) recognize digital manufacturing as a major shift in the way pharmaceuticals are manufactured that stresses function validation in the interest of patient safety, product quality, and regulatory compliance. The FDA recommends a risk-based

approach to validating AI and machine learning-based models used in digital manufacturing, explaining that models used to assist in manufacturing processes must be transparent, reliable, and monitored over their entire lifecycle. Similarly, the EMA also requires robust validation processes with an emphasis on appropriate documentation, oversight of risk management, and ongoing evaluation over the model's lifecycle to confirm digital tools and models are operating as intended without sacrificing product quality. Both organizations emphasize the need to comply with Good Manufacturing Practices (GMPs) and the need to maintain electronic system records, which requires that manufacturers understand that digital processing systems and tools are validated to continue generating compliant, trustworthy, quality pharmaceuticals to be distributed through the supply chain [15].

2. 3D PRINTING

Though the first 3D printer was available commercially in 1988, 3D Printing can still be considered as a newer approach to the pharmaceutical industry [16]. Recently, the technique has been increasingly recognized in medicine, but the major application still lies in medical devices rather than in drug manufacturing. This is why many authors have stated that in the pharmaceutical industry, 3D printing is still in the stage of infancy [17]. The first 3D printed drug was approved by the FDA in 2015, which was named as SPRITAM[®]. SPRITAM[®], produced by binder jetting, is the 3D printed product containing 1,000 mg of levetiracetam [18]. The 3D printing technique has found its applications in various dosage forms and medical devices. In the oral delivery, the controlled release dosage forms and the site-specific dosage forms are also being 3D printed [17]. In addition, various methods are available in the market to carry out these processes. These methods are listed below [19]: Fused deposition modelling (Ink-based technologies), Inkjet printing (Laser-based methods), Selective laser/heat sintering, and Stereolithography.

In their article, Ramola *et al.* [20] have reviewed the trends in the research of 3D printing within 10–11 years, starting from 2007 to 2018. The article gives the basic idea about the use and cost-effectiveness of the additive manufacturing methods, and it also mentions a list of 70 articles that have been studied by

the authors. 3D Printing, also known as additive manufacturing or freeform fabrication technology or rapid prototyping technique [21], converts a 3D model to a physical model using a layer-by-layer manufacturing technique.

A thorough review highlights the changing nature of pharmaceutical manufacturing through 3D Printing, focusing on the use of bioinks, implementation of AI-controlled process optimizations, and lowering costs on personal medication. The review also discusses creating drug-release, unique patient profiles, and increased medication adherence and effectiveness over conventional ways of providing medication [22]. Another review discusses recent advances in the pharmaceutical 3D printing sector, on the advent of new APIs, cost modeling, and new additive manufacturing techniques, taking into consideration practical aspects and regulations surrounding practical work being done through 3D printing [23]. Another paper on advanced 3D printing technologies emphasizes the effects on orthopedic implants, the advantages of bioprinting for creating patient-specific designs, and reductions in overall healthcare costs through material efficiency, revisions of prior surgeries, and streamlined surgical workflows [24]. Considering the general process of 3D printing, the steps are as follows (Fig. 1) [18].

The processes in 3D printing where computers actually come into the picture are the initial steps, where the product design is rendered on a digital format. The fundamental concept behind using computers in 3D printing is that the user will finalize the format using computer software, and this format will guide the printer to print the medicine. Hence, the bottom line is that the computers form a core of the 3D printing process, which drives the actual mechanical printing process. Using the computer-aided software, the product can be designed either in 3D format or 2D format. If the design is in 3D format, the layers will be seen directly as one over the other, but in 2D format, the design has to be provided in a series of images that are arranged in a manner such as to produce the respective layers. Once the computer-aided format is ready, it has to be converted to a file that is machine-readable. The Standard Tessellation Language (STL) files are usually the ones in which the 3D models are converted. These files give the surface outlines of the design [19]. The 3D printing programs are then used to slice the surface

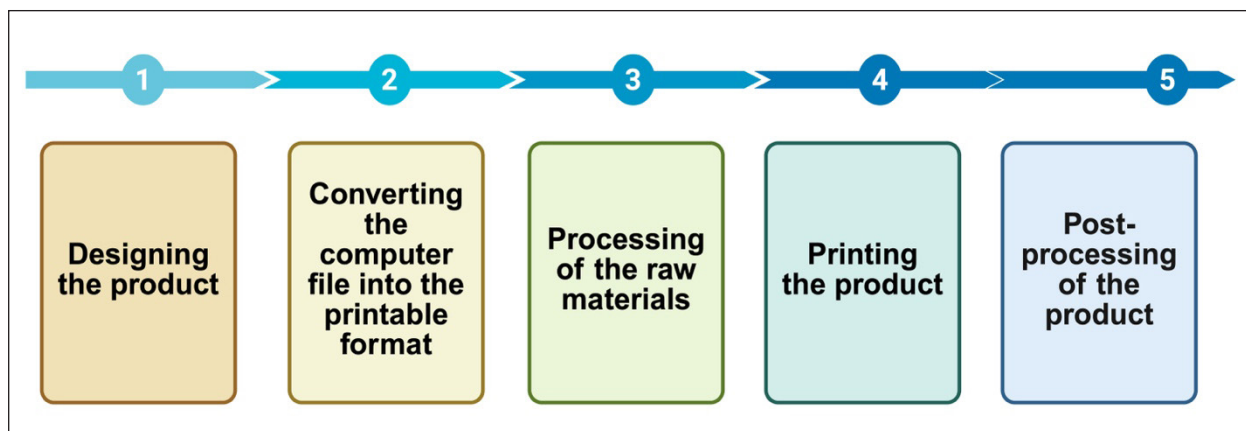


Figure 1. Process of 3D printing.

Table 1. 3D printing techniques in pharmaceutical formulation, focusing on process type, advantages, and limitations.

Printing technique	Process type	Advantages	Challenges
Fused deposition modeling (FDM)	Nozzle-based extrusion	High mechanical strength, accessible excipients, suitable for solid dosage forms	Requires prefabricated filament, high printing temperature (not ideal for thermolabile drugs)
Direct powder extrusion (DPE)	Nozzle-based extrusion	No filament prefabrication, robust output	High temperature can degrade drugs, powder heterogeneity
Semisolid extrusion (SSE/PAM)	Nozzle-based extrusion	Low temperature (good for sensitive APIs), cell-friendly	Poor mechanical strength, need for solvent removal post-printing
Stereolithography (SLA)	Laser photopolymerization	Excellent resolution, low temp for drug stability	The toxicity of resin requires post-printing cleaning and curing
Selective laser sintering (SLS)	Laser sintering of powders	No solvent needed, high print resolution	API degradation risk due to laser, excess waste

into thin printable layer cross sections. For example, Zidan *et al.* [25] used the Perfactory[®] software Suite (EnvisionTEC Inc., Dearborn, Michigan) to slice the geometric 3D format into desired layer thickness while formulating a semisolid formulation. There are a few other software programs available for some of the 3D printing methods that automatically guide the printing position of the scaffold [18]. 3D printing techniques in pharmaceutical formulation, focusing on process type, advantages, and limitations, are given in Table 1.

Junk and Kuen [26] have summarized the use of CAD tools in their work, so that users with no experience in this area can know the basic requirements as well. The authors have also studied five different CAD software and evaluated them for their ease of use and the comprehensive range of functions. Huanbutta and Sangnim [27] successfully formulated a metronidazole-loaded floating controlled-release tablet using the 3D printing technology. The housing of the floating tablet was designed geometrically using computer-aided software named SketchUp 2017. The software-guided housing was successfully printed using fluid deposition modelling.

Key players in the area of 3D-printed drugs include Aprecia Pharmaceuticals, Triastek, MB Therapeutics, Laxxon Medical, FabRx Ltd, CurifyLabs, and Multiply Labs. These companies are advancing the use of different additive manufacturing technologies for drug design, which involves patient-specific doses, rapid prototyping, and complex drug release mechanisms. At present, the sole fully approved and commercially available 3D-printed drug is Spritam[®] (levetiracetam): Produced by Aprecia Pharmaceuticals and approved by the FDA to treat epilepsy (partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures), this drug rapidly disintegrates in the mouth to facilitate swallowing, which is helpful for patients who have difficulties swallowing. Other 3D-printed drugs are in clinical or investigational phases and are not currently available on the market, such as Triastek's T22: For chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension, which has received FDA investigational new drug clearance [28].

Even with rapid progress in technology, regulations surrounding 3D printed pharmaceuticals are still in transition. 3D-printed medicines do not have well-established regulatory standards, like more traditional dosage forms, surrounding quality control, validation, GMPs, and approval. The FDA has released some technical considerations for 3D-printed

medical devices and has authorized the marketing of the first 3D-printed drug (Spritam), but there are no comprehensive, uniform pharmaceutical regulations yet written for 3D-printed medicines. In addition, it leaves manufacturers with uncertainty about process validation, product release, and continued oversight of their products [22].

There are specific challenges to moving 3D printing processes from a lab proposition to a full-scale industry proposal. Although 3D printing currently remains a terrific method for generating small, individualized, patient-specific batches, its positives are overshadowed by limitations in print speed and replicability when the goal is to progress toward a broader, robust scale environment. Efforts are being made to improve upon multinozzle systems, along with changes to print resolution, but it still raises a question of whether they would be as efficient and cost-effective as traditional batch manufacturing [29].

3. ARTIFICIAL INTELLIGENCE

AI is one of those techniques that has recently been established and expanded in various industries. Likewise, the pharmaceutical industry, which still has plenty to discover, does not remain behind in the application of AI in any of its domains. As the scientists are discovering more and more about this field, more is becoming its requirement, particularly in the field of optimization, which is obligatory in the formulation and development of any dosage form. The process of optimization has traditionally been carried out using a 'change-in-one-parameter-at-a-time' system, or simply called a trial-and-error basis. Since this system was found to consume a lot of time as well as materials, a better system was required for the optimization process to consider more than one parameter at a time, and also be simplified at the same time. Hence, the introduction of AI to this field has shown a promising future in formulation and development by making the process time as well as cost-effective [30].

3.1. Expert systems

The expert systems are comparatively recently discovered domains of AI. The expert systems were developed to mimic the problem-solving ability of humans by using computer models. These systems are famous as user-friendly tools as they extract the knowledge from experts and present it to the users. In this way, comparatively less knowledgeable people

in the field can easily find the solutions to their problems. Users have the facility to interact with the system, and this interaction is called the “front-end interface”. This way, the users can consult the system regarding the problems, and the system will guide them by asking the related questions and extracting the desired information from their end. The knowledge base and the reasoning system make up the foundation of expert systems. Knowledge base stores the knowledge of experts related to the field, and the reasoning system uses the methods based on logical reasoning to come up with the solution [31]. The reasoning system is popularly called the inference engine. Apart from these two constituents, expert systems include man-to-machine interfaces. To achieve these features, programmes are supposed to be written. These programmes can be written in simple computer languages, special-purpose languages, or shells and toolkits [32]. Shells and toolkits are the prewritten programs, which, upon activation command start working as expert systems. Once the system is run, the user will either get a solution at the end or the system will give the result saying the solution is not available [31].

The best example of an expert system is the SeDeM expert system. This system is usually used in the preformulation techniques. The SeDeM diagram expert system was mentioned in the research works in 2005. Afterwards, the system did not gain much attention till 2012. But after this period, researchers began to understand the importance of the system. And the system’s applications were found to have increased rapidly. These systems have found their major applications in preformulation studies, including determining how much and which ingredients should be taken to get a good compressibility [33]. Researchers often receive access to SeDeM through partnerships with academia, pharmaceutical technology service providers, or downloadable templates that are made available in scientific publications. Once access is granted, the user conducts the necessary powder testing, inputs the data, and evaluates the data to determine formulation weaknesses and the amount of excipients needed for the desired tablet formulation. Ultimately, the SeDeM Expert System helps with time- and cost-efficient formulation development through a unique quantitative and visual aid to the suitability of powders for direct compression. The SeDeM diagram expert system is depicted in Figure 2 [34].

3.2. Artificial neural networks

Pharmaceutical formulation using computer-aided engineering techniques and artificial neural networks (ANNs) is a new paradigm for the next generation of more efficient and less expensive drug manufacturing processes. Integration of ANNs allows the modeling of complex and nonlinear actions in pharmaceutical formulation results, which in turn can lead to predictive rather than qualitative experimentation. For example, one important case study designed a pharmaceutical dosage form in the form of a tablet for a poorly soluble BCS Class IV drug using ANN-based modeling methods within a QbD framework. In this case study, an ANN with five hidden nodes was trained to predict critical quality attributes like drug particle size distribution, which is an important aspect for the bioavailability of the drug. The ANN accurately predicted *in vitro* bioavailability ($R^2 > 0.94$) and guided the process

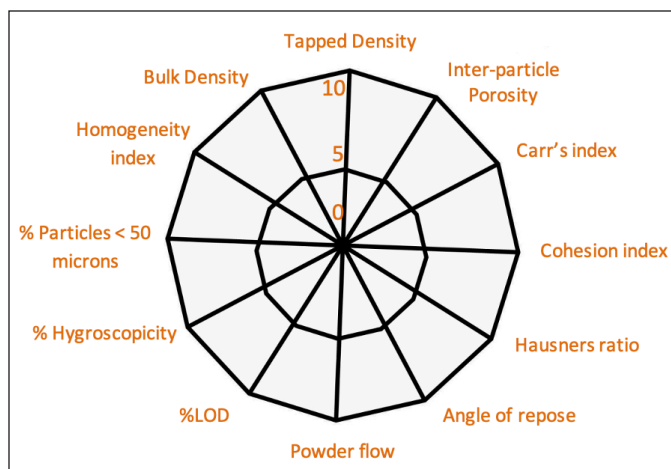


Figure 2. SeDeM diagram expert system.

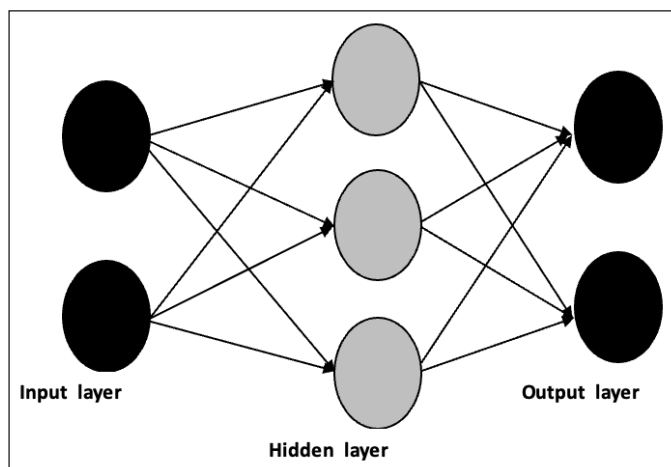


Figure 3. Structure of an artificial neural network.

parameter optimization, resulting in multiple GMP batches with *in vitro* dissolution profiles closely matching model predictions. All of these formulations subsequently met bioequivalence specifications for FDA trials under all testing conditions, thus enhancing the confirmatory application of ANN-based formulation models [35].

ANN is that part of AI that tries to mimic the neural connections that are present in the human brain. In 1991, the ANNs were introduced to the field of pharmaceutical formulations by Hussain *et al.*, [36] and have been progressing in their use to date. The authors usually mention ANNs as empirical nonlinear tools that are mostly used for their predictive ability. The ANNs are marked with major advantages; two of which are the capability of self-learning and the other one is their multidisciplinary nature [37]. ANNs find different applications in this field, such as recognizing patterns, to cluster and modeling the data, carrying out approximation functions, choosing the optimum gradient conditions in chromatography, designing and filtering the preformulation data, and predicting the drug activity [38]. The structure of an ANN is depicted in Figure 3.

4. COMPUTER SIMULATIONS

Computer simulations are an effective way to connect theoretical predictions to experimental results in pharmaceutical formulation. By simulating the behaviors, stability, and release profiles of drug formulations under a variety of conditions, researchers can make predictions about the essential characteristics of the formulations (e.g., solubility, dissolution, and the pharmacokinetics of the formulation) before completing actual experiments. Predictions of this nature enable fine-tuning of the formulation, change to the exact excipient that will be the most suitable, and inform about the stability and compatibility issues, before even setting foot in the laboratory. The results from these virtual models will direct experimental design, inform the need for costly trial-and-error, and help facilitate the transition of potential formulations to clinical paradigms, enhancing drug development precision, efficiency, and cost effectiveness [39].

Digital twins and physiologically-based pharmacokinetic (PBPK) modeling are transformative tools that are enabling the development, real-time simulation, and optimization of drug development and delivery methods in new ways of formulation science. Digital twins provide virtual duplications of a manufacturing process or a patient's physiologic system that can be used for process optimization, predictive maintenance or personalized medicine, whereas PBPK modelling predicts a drug's absorption, distribution, metabolism, and excretion *in silico* reducing the need for

Table 2. Comparison of predictive accuracy between AI techniques and RSM [41].

Method	Predictive accuracy	Key notes
AI (ANN, ML)	High	Captures complex nonlinear patterns
RSM	Moderate	Best for simpler, linear relationships

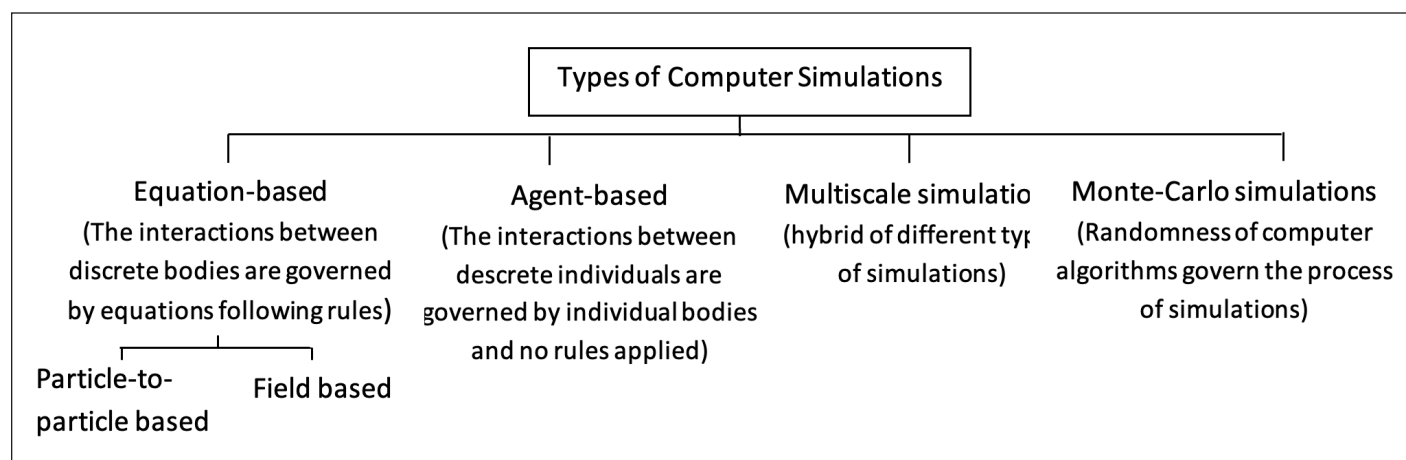


Figure 4. Types of computer simulations.

Table 3. Simulation model categories [42].

Sr. No.	Model	Purpose	Example
Continuum models			
1	Solid mechanics	To model the compaction of powders	Simulating the compaction of MCC tablets to test the friction between powder and die wall
2	Heat and mass transfer	To study the mechanisms based on the temperature gradients or the concentration gradients	To simulate the portions in the lyophilization process
3	Fluid dynamics	To simulate the flow of substances that can be considered as fluids	To simulate the dense and mixing powder flow
4	Inhalation modelling	To simulate the delivery of pharmaceuticals to the lungs	Simulating the tracheo-bronchial pathway
5	Spray drying	To simulate the drying process using the spray drying technique	Improving the final quality of the product by modifying the gas flow rate using spray drying simulations
6	Granular material flow	To simulate the flow of powders or granules	Simulating the flow of powders during compression
Discrete models			
7	Hard sphere model	Simulating the applied forces on a particle during the collisions as an implementation of Newton's second law	To investigate the rapid flow of the powders through inclined tubes
8	Soft spheres model	To simulate momentum change and displacement change during the collision among particles	To simulate the behaviour of the powder during the filling of the die or the compaction of the powder

animal studies or labor intensive lab work, and an improved candidate selection and dosing strategy [40]. Types of computer simulations are given in Figure 4.

Since the simulations are computer-driven, it is very important to verify and validate these systems so as to keep the accuracy of these models intact. The verification is carried out for two constituents of these models, namely verification of the solution, which verifies the output given by the model, and verification of the code, which verifies the algorithm used in it. The verification is done by observing how finer the discretization grid is. This requires the resolution of time and space to be checked. The validation is carried out by comparing the simulated data with the experimentally observed data [41]. Comparison of predictive accuracy between AI techniques and RSM is given in Table 2. In their review article, Kremer and Hancock [42] studied the simulation numerical models used in the different dosage form developments. They classify these models into two categories: Continuum models and Discrete models. Table 3 briefly describes these models.

5. FUTURE PROSPECTS

The next steps in computer-aided pharmaceutical formulation should focus on closing the gap that exists between US predictive modeling with AI technologies, chemoinformatics-based molecular and formulation design, and *in silico* pharmacokinetic optimization. Connecting these spatial and temporal domains through interoperable data platforms and cutting-edge simulation tools would enable multiscale modeling capabilities from the molecular interaction level to the systemic drug interaction level. Furthermore, research priorities would consist of establishing standardized datasets for training AI technologies, confirming *in silico* predictions with *in vitro*–*in vivo* correlations, and engaging in interdisciplinary scientific collaborations between computational scientists, formulation chemists, and pharmacokinetic scientists to speed the progression and rational nature of drug development [43].

6. CONCLUSION

Considering the importance of technology in the field of pharmacy, the above-described techniques, 3D printing, AI, and computer simulations have proved their worth in making the dosage form manufacturing process easier. 3D printing can be seen establishing itself in continuous manufacturing in the coming days, which will only be possible with the help of strong processing computer technologies, which form the basis of the technique. Researchers have been investing in developing the software as well as converting file formats so that complex information can be processed and converted efficiently into a readable format by minimizing the hidden errors. Likewise, the computer simulations that are widely used to imitate the processes that occur inside the body also have a strong potential in imitating the formulation processes and predicting the related results. This area has not yet been used to its full degree, however, and remains a sector that still needs to be exploited. On the other hand, while the AI systems are current attractions for many industries and have been explored to a greater extent,

their reach here is not restricted. It is well understood by now that AI has a huge contribution in reducing the time and resource expenditure in the development process. AI tools illustrate their utility in all possible aspects of the drug development process, taking into account the majority involvement in preformulation and optimization studies. Nevertheless, the developments in this field are still being worked upon and are limitless. It is assumed that the more gaps in the field more will be the scope for development and hence the greater the progress. Ultimately, all these strategies can be seen as taking the revolutionary step in the field of pharmacy. As the field is gradually moving towards technical developments, pharmaceutical professionals may get worried about these techniques taking over their employment. However, it is very important to understand that to develop and establish these techniques, the most important thing still remains the creativity, imagination, intelligence, and expertise of human brains. Such innovations should therefore be seen as instead of taking over the jobs, generating even more competitive prospects and opportunities in the future.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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10. CONFLICTS OF INTEREST

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11. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

12. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

13. PUBLISHER'S NOTE

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14. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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