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Artificial Intelligence in Design, Optimization, and Performance Prediction of Pharmaceutical Formulations: A Paradigm Shift in Development of Nanomedicines

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Opinion

The introduction of the nanomedicine approach in the past two decades has led to a paradigm shift in the development of novel drug delivery systems. However, despite its great potential and significant improvement in therapeutic efficacy and safety at the preclinical stage, the researchers are still skeptical regarding the translation of nanomedicine into the clinical application. The primary reason for the low clinical success of nanomedicine is the reproducibility of the formulation of nanosized delivery systems, the performance of these systems in the complex in-vivo vascular system, and ultimately their safety profile and in-vivo fate. Besides, the industry may also face disparate limitations in nanomedicine translation like higher R&D cost, low scaleup potential, and lack of process efficiency. Recently, artificial intelligence has gained enormous attention as an efficient tool for formulation development. Artificial intelligence (AI) is the simulation of the human cognitive traits exhibited by any machine that utilizes the personified knowledge to provide solutions to specific complex problems while simultaneously learning from the solutions, creating a newer generation of information and thereby achieving a higher precision level. The amalgamation of these two distinctive fields has shown remarkable improvement in the process of formulation development [1].

In recent years, AI integrated with tools to recognize the statistical pattern, biological data sets, mathematical models, and probability and economic theories has been explored for their application in the development of nanomedicine, which conventionally is a tedious and expensive process due to the multifaceted design and in-vivo variability in the performance of nanosized systems. AI programs provide a new alternative that expedites the development of nanomedicine with minimal experimentation, thus reduces the cost and development time significantly. AI provides rapid analysis of complex functions including a large number of biological variables and also performs functions like prediction, interpretation, and management of functions or data with high accuracy. AI-based approaches also address the limitations of the design of experiment (DoE) conventionally used for the optimization of drug delivery systems. The DoE, albeit widely employed exhibits inaccuracies in the polynomial models which results in the lower confidence level in the trends rendering the calculations uncertain. In addition, a lack of comparative studies and models limits the experimental outcomes [2]. The predictability of Artificial neural network (ANN) based models may reduce these uncertainties and limitations as it enables the analysis of complex physiological relationships that exhibits a high degree of variability and non-linearity, often seen in pharmaceutical research like; formulation development and optimization, design of pre-formulation studies, and predict the behavior of drugs. The dynamic type of neural networks makes predictions based on past information that might play an important role in characterizing or modeling controlled release formulations. The prediction of the size and distribution of the polymeric nanoparticles using the QSPR modeling based phase behavior model, alongside the prediction of in-vivo behavior of

lipid-based systems by dynamic lipolysis model (DLM) are few of the examples of the application of AI as tools in formulation development.

Machine learning (ML) algorithms, another important tool that may decrease the failure rate and minimize the associated cost by providing a better prediction of data points to predict the physical stability. Therefore, the combined approach of experimental and molecular- modeling as a novel prediction model for determination of the product stability has been reported for solid dispersions where the random forest (RF) model determines the effect of process parameters on stability was predicted [3]. Similarly, the molecular modeling-based prediction of formulation-excipients interaction and its impact on stability has also been reported [4]. Machine Learning methods may be used as an effective tool for the identification of potential transdermal enhancers, thereby significantly reducing the chances of failures and increasing the efficiency of the formulation design approach. The machine learning-based approach for prediction of percutaneous absorption of exogenous molecules has been reported to provide accurate enhancer type by predicting the enhancement ratio of the drug permeating through the skin in simulated conditions [5].

There are numerous instances where AI tools have been used in the design of the algorithms for the identification and evaluation of physicochemical parameters which affect quality attributes of nanomedicine like; nanoparticle size, loading efficiency, cytotoxicity, stability, or size of nanoparticles. The prediction of the size and distribution of the polymeric nanoparticles using the QSPR modeling based phase behavior model, alongside the prediction of in-vivo behavior of lipid-based systems by dynamic lipolysis model (DLM) are few of the examples of the application of AI as tools in nano formulations development. Various studies of AI-based construction of correlation between the entrapment efficiency and binding energy of the drug to polymer, stability of nano emulsion and surfactant concentration, etc. have been reported in the past. AI guides in the prediction and design of functional nanoparticles with ideal bioactivity, their optimization, prediction nano-bio interactions (interaction with enzymes, cell membrane, immune system, vasculature, and potential targets), and determination of the nanotoxicity, overcoming the uncertainty and limitations [6-8]. The design of nanomedicine for immunotherapy can be optimized using a machine learning-based approach. To predict the antibody-excipient interactions via top surface characteristics identifications a machine learning-based tool has been reported which aided in finding the affinity of excipients to interact with the regions of the mAb surface subsequently responsible for possible aggregation and viscosity behavior. Precision nanomedicine in cancer therapy has also gained attention in the past few years, where AI has a significant role to play. The AI-based algorithms provide pattern analysis and consider genetic heterogeneity in individual patients to design a rational theranostic platform for more accurate and precise therapy and diagnosis. Besides, it also provides simulation-based predictions about the in-vivo performance of the formulation in individual patients. AI can also provide accurate predictions and optimization of the processing parameters, for stimuli-responsive nanomedicines for targeted delivery of therapeutics.

The critical aspect of targeted nanomedicine is the design of stable linkers used in the functionalization of nanosized systems to ensure a specific and selective release profiles of therapeutic payload. Application of AI-based computational tools in the rapid, accurate, and precise identification of appropriated linker groups and the development of conjugates of the drug using the identified linker for enhancing their therapeutic potency and alleviating the toxic effects. Besides, the machine learning-based prediction of performance, optimization, and functioning of nanorobots for theranostic applications and drug delivery exhibits great potential. The application of AI-based simulation and modeling techniques have been instrumental in the development of these nanorobots. The rule structures of nanorobots that govern the behavior and motion of these robots can be controlled by AI-based technologies.

AI is a superior tool in predicting the in-vitro and in-vivo correlations (IVIVC) without in-vivo data in comparison to the conventional regression approach as it can establish complex relationships and incorporate numerous variables without a predefined model structure [9]. The machine learning algorithms are also capable of predicting the pathogen-drug dynamics, most suited dosage regimen, and most efficient drug delivery methods [10-13]. Furthermore, predicting the physicochemical and pharmacokinetic properties [14], non-linear drug absorption by using the molecular structure descriptors, and drug-target interactions by FRnet-DTI [15], semi-supervised link prediction classifier, similarity/distance, matrix factorization, feature and network based methods [16], and regularized least squares classifier [17] are few other uses of AI-based tools in the prediction of the performance of the drug delivery systems. Evaluating the preclinical safety and predicting the clinical outcome is also a quintessential aspect of formulation or development. The animal models used for the establishment of preclinical safety and efficacy are not only costly and tedious, but it also has significant ethical limitations. The low successful translation of new drugs and formulations due to inaccurate estimation of performance parameters in the initial drug development phase, alongside the genetic variations and inconsistent individual response are a few of the major limitations of conventional methods used in the development of the drug or dosage form. Machine learning and deep learning (DL) tools have also found their role in predicting the preclinical and clinical performance of the dosage form including side-effects, adverse drug events, accumulative potential, the possibility of dose dumping, and their biological fate [18]. Currently, support vector machines (SVMs), ensemble approach like the RF that combines various ML tools, and DL tools like deep convolutional neural networks (DCNNs) are few of the computational tools for safety assessment, compounds screening, and drug target interaction study, that have been reported to

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exhibit a high degree of accuracy, precision, and robustness [19-21].

Conclusion

AI-based tools have the potential to improve the efficiency, expedite the process, and reduce the cost of drug/formulation development process. Numerous pharmaceutical industry giants have either already acquired artificial intelligence technologies or collaborated with the AI-based R&D firms. AI can bring a paradigm for cost-effective and rapid development of nanomedicines and therapeutics with minimum experimentation, with accurate and precise performance prediction hence improving the translational potential of novel therapeutics. However, the process of drug discovery and formulation development has traditionally been the experiment and evidence based. Therefore, the integration of AI-based technologies with the formulation development process at the fundamental level still requires significant work prior to its implementation as an intrinsic and reliable tool.

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