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Artificial intelligence-aided rational design and prediction model for progesterone-loaded self-microemulsifying drug delivery system formulations

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ABSTRACT

Artificial intelligence (AI) is now applied across various domains in nanomedicine. Self-microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of active compounds that can produce spontaneous oil-in-water emulsions. SMEDDS can improve the solubility of lipophilic drugs such as progesterone (PG). However, the physicochemical properties of SMEDDS are sensitive to various factors, depending on their components. This study generated a prediction model algorithm for PG-loaded SMEDDS to provide appropriate droplet size (DS), polydispersity index (PDI), zeta potential (ZP), and % drug loading (%DL). Various machine learning algorithms were compared for their accuracy, as reported by root mean square error (RMSE) and coefficient of determination (R^2). The selected machine learning algorithms were implemented with an unseen training dataset, and the model performance was re-evaluated. The correlation of each factor was investigated. Self-micro emulsifying (SME) time, cloud point, pH, and viscosity of predicted PG-loaded SMEDDS were evaluated. Results showed that linear regression algorithms gave the highest accuracy and optimal prediction performance with the highest RMSE and R^2. All components of PG-loaded SMEDDS correlated with DS, PDI, ZP, and %DL. The physical properties of predicted PG-loaded SMEDDS showed SME time within 39 s, cloud point at around 71.3 °C, pH between 5.53 and 6.10, and viscosity between 10.32 and 14.23 cP. This research outlined the application of a machine learning algorithm to build a prediction model to optimize PG-loaded SMEDDS drug delivery formulations.

Keywords: artificial intelligence; machine learning; prediction modeling; progesterone; self-microemulsifying

1. INTRODUCTION

Pharmaceutical research and development have now embraced the use of artificial intelligence (AI) in nanomedicine, encompassing technologies such as liposomes, solid lipid nanocarriers, niosomes, and self-microemulsifying drug delivery systems (SMEDDS). The fusion of AI and nanotechnology addresses intricate challenges in drug discovery, drug delivery, and personalized interventions. This integration shows immense promise for revolutionizing the processes of drug research and development (Tao et al., 2021). Traditional

drug development pipelines often face disadvantages such as high resource utilization and prolonged time consumption. AI algorithms, endowed with the ability to analyze vast datasets rapidly and precisely, play a crucial role in identifying novel formulations and predicting their potential efficacy. This collaborative approach, where AI and nanomedicine converge, not only accelerates drug development but also enhances its efficiency. By overcoming challenges inherent in traditional methods, this synergy brings about a transformative shift in the landscape of pharmaceutical innovation (Dasta, 1992; Han et al., 2023).

The process of AI encompasses problem-solving, learning, pattern recognition, and decision-making. AI systems employ algorithms, data, and computational capabilities to imitate or reproduce human cognitive functions such as reasoning, problem-solving, and perception. Various techniques of AI technologies include machine learning, neural networks, and deep learning. These methodologies empower AI systems to screen and interpret extensive datasets, identify intricate patterns, make predictions, and enhance their performance progressively through training and accumulated experience (LeCun et al., 2015; Vora et al., 2023).

Nanomedicine involves using nanoscale materials within the particle size range of 100 to 1000 nm, serving as devices to optimize drug delivery and overcome barriers such as poor solubility, thereby maximizing target effectiveness (Soares et al., 2018). One type of nanomedicine, known as SMEDDS, constitutes an isotropic mixture comprising an active compound, lipids, surfactants, and co-surfactants. This mixture can spontaneously produce oil-in-water emulsions when moderately agitated in an aqueous phase. The SMEDDS system can enhance the solubility of lipophilic drugs classified under the Biopharmaceutical Classification System (BCS) as class II and IV and prevent drugs susceptible to hydrolysis (Dokania and Joshi, 2015; Mandić et al., 2017; Ujhelyi et al., 2018). Progesterone (PG), an extremely hydrophobic drug with a log P value of 3.9, exhibits very low aqueous solubility of approximately 10 mg/mL PG was classified as a class II drug by the BCS and labeled as 'practically insoluble' by the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.) (Javadzadeh et al., 2007; Yalkowsky et al., 2010). PG is an endogenous steroid sex hormone that plays a crucial role in the menstrual cycle, pregnancy, and embryogenesis in humans (Nagy et al., 2021). PG influences the production of inflammatory mediators, diminishes metabolism disorders and vasomotor symptoms, prevents cardiovascular disease (Prior et al., 2014), and acts as a neuroprotective agent in the brain, slowing the progression of Alzheimer's disease (Singh and Su, 2013). Therefore, we selected PG as a model for lipophilic drugs in this study.

In this exploration of the convergence of AI and nanomedicine in pharmaceutical development, various prediction model algorithms were generated to develop PG-loaded SMEDDS to provide appropriate droplet size (DS), polydispersity index (PDI), zeta potential (ZP), and % drug loading (%DL). The formulations were adjusted to achieve the precision of personalized medicine while maintaining appropriate properties and efficacy. This study redefined the boundaries of pharmaceutical innovation and heralded a new era in patient-centric healthcare solutions.

2. MATERIALS AND METHODS

2.1 Materials

Micronized progesterone (PG) was supplied by Enviero, Michigan Facility (Kalamazoo, USA). Eugenol was received from Bruno Court (Grasse, France). Labrasol® (caprylocaproyl polyoxyl-8 glycerides) was received from Gattefossé (Lyon, France). Absolute ethanol was purchased from Sigma-Aldrich (Missouri, USA). All other chemicals and solvents used were of analytical grade.

2.2 Preparation of PG-loaded SMEDDS

The SMEDDS formulation was prepared by mixing eugenol, Labrasol®, and ethanol obtained from a previous microemulsion experiment study, selected based on a pseudo-ternary phase diagram (Aumklad et al., 2022). After mixing until a homogeneous solution was achieved, 20% w/w of PG was dissolved in the SMEDDS. The PG-loaded SMEDDS was thoroughly mixed using a vortex mixer to obtain uniform, transparent, clear formulations. The excess PG from PG-SMEDDS was centrifuged at 14000 rpm for 20 min at 25 °C. The PG-loaded SMEDDS was evaluated for DS, PDI, ZP, and %DL, and the results were recorded as a dataset. Thirty PG-loaded SMEDDS formulations were prepared, as listed in Table 1, with raw data provided in Supplementary Data S1.

Table 1. The component range concentration of PG-loaded SMEDDS formulations

SMEDDS components	Rang of concentration
Eugenol (%)	20 – 40
Labrasol® (%)	15 – 30
Ethanol (%)	32.25 – 60

2.3 Characterization of PG-loaded SMEDDS

The dynamic light scattering (DLS) technique, utilizing a Zetasizer Nano Series (Malvern Instruments, version 4.10), was employed to determine the DS, PDI, and ZP. For each PG-loaded SMEDDS formulation, a microemulsion was initially formed by diluting 100 times with water and then mixing using a vortex mixer to achieve a uniform droplet distribution. The formulation was then filled into a disposable folded capillary cell and measured. All measurement settings were carried out at a 90° angle to the light beam and at 25 °C (Suriyaamporn et al., 2023).

2.4 PG content assay using HPLC

The determination of PG was conducted using HPLC. The samples were appropriately diluted with methanol and filtered using a 0.45-µm syringe filter. Chromatographic separation was achieved using a Zorbax Eclipse XDB-C18 column (250×4.6 mm, 5 µm pore size, Agilent, United States) with temperature set at 30 °C. The mobile phase consisted of 90% v/v methanol and 10% v/v ultrapure water, flowing at a rate of 1 mL/min, with detection carried out at a wavelength of 240 nm. The retention time for PG was approximately 4.4 min (Biruss and Valenta, 2008). The calibration curve was plotted using five different concentrations of PG for analysis. The PG assay percentage was calculated following Equation (1).

$$\%DL = \frac{\text{Quantified amount of PG in SMEDDS}}{\text{Amount of PG added to the formulation}} \times 100 \quad (1)$$

2.5 Generation of PG-loaded SMEDDS dataset

In this study, the dataset of PG-loaded SMEDDS was generated randomly by a computer program. The components of PG-loaded SMEDDS such as eugenol, Labrasol®, and ethanol were mixed in various concentrations following Table 1, modified from a previous study (Aumklad et al., 2022). The components of PG-loaded SMEDDS were labeled as input data. Thirty formulations of PG-loaded SMEDDS were measured for DS, PDI, ZP, and %DL as output data. After completing all experiments in the preprocessing step, the dataset was cleaned by detecting outliers and normalized for data analysis to generate a prediction model. Visualization of the dataset was observed to describe the trend of data and the physicochemical properties of PG-loaded SMEDDS.

2.6 Prediction model formulation using machine learning

The critical factors impacting PG-loaded SMEDDS which affected DS, PDI, ZP, and %DL were eugenol, Labrasol®, and ethanol. The predictability of output data depending on these critical factors involved the application of various machine learning algorithms such as linear regression (LR), polynomial regression (PR), support vector regression (SVR), K-nearest neighbor regression (K-NN), Gaussian process regressor (GPR), and neural networks (NN) on the prepared dataset adapted from a previous study (Öztürk et al., 2018). The machine learning algorithms were run with default parameter settings. The prepared dataset was applied to each machine learning algorithm with cross-validation to avoid overfitting of the prediction model. The performance of the machine learning algorithms was evaluated by root mean square error (RMSE) (Equation (2)), describing the differences between actual experiments and prediction data, and coefficient of determination (R^2) exceeding 0.5. To analyze the correlation of data, Spearman's rank correlation coefficient was reported as a correlation matrix. The machine learning algorithms were developed using RapidMiner Studio version 10.3 and PyCharm version 2023.3.2. A p-value less than 0.05 was considered significant.

$$RMSE = \sqrt{\sum_{i=1}^{N} \frac{(X_i - \hat{X}_i)^2}{N}} \quad (2)$$

2.7 Implementation and assessment of the prediction model

The five new randomly unseen testing datasets of PG-loaded SMEDDS were formulated and remeasured. The unseen testing datasets were obtained from the random components of PG-loaded SMEDDS, which were never trained in the AI model. All output data were applied to the optimal prediction model from a previous study, and model accuracy was evaluated by RMSE. Five formulations with DS < 300 nm, PDI < 0.4, ZP < -30, and the highest %DL were selected for further evaluation. The criteria of PG-SMEDDS were determined from a previous study to adapt to the AI model selection. All criteria represented the appropriate physical properties in SMEDDS (van Staden et al., 2020).

2.7.1 Self-emulsification time (SME time)

The self-emulsification time refers to the duration needed to achieve a clear and transparent microemulsion when PG-loaded SMEDDS were combined with water. For each PG-loaded SMEDDS formulation, 0.1 g was added to 25 mL of phosphate buffer solution (PBS) at pH 7.4. The mixture was maintained at 37 °C with gentle agitation using a magnetic stirrer set at 50 rpm. The time taken for complete self-emulsification, resulting in a clear physical appearance was recorded.

2.7.2 Cloud point (T_{Cloud})

The assessment of the impact of temperature on the phase behavior of microemulsions involved determining the cloud point (T_{Cloud}) to evaluate the storage stability of PG-loaded SMEDDS formulations. The cloud point, indicating the temperature at which the formulation becomes turbid, was examined. In brief, 0.1 g of each PG-loaded SMEDDS formulation was dispersed in 25 mL of PBS at pH 7.4 and allowed to stabilize. The PG-loaded SMEDDS formulations were then subjected to gradual temperature increases in a water bath and the temperatures at which the clear samples turned turbid were recorded.

2.7.3 pH

The pH of each PG-loaded SMEDDS formulation was measured using a pH meter (Laquatwin Horiba, Kyoto, Japan) at 25±2 °C to ensure that the formulation was suitable for application and non-irritating.

2.7.4 Viscosity

The viscosity of the PG-loaded SMEDDS was evaluated using a viscometer equipped with a stainless-steel spindle SC4-18 (Brookfield DV2T; Toronto, Canada) at 100 rpm (60–80% torque) at 25±2 °C. Then, 7 mL of each PG-loaded SMEDDS was filled into the sample chamber and the viscosity was measured at three points every minute.

2.7.5 *Statistical analysis*

The machine learning algorithm generated a prediction model using RapidMiner Studio version 10.3 and PyCharm version 2023.3.2. The cross-validation process was considered successful if the attained R^2 value exceeded 0.5. To evaluate the predictive performance of the model, RMSE was applied. The research was conducted in triplicate, and the results were presented as mean ± standard deviation (SD). The two-sided independent t-test was employed to compare the two groups, utilizing SPSS® software version 19 (SPSS Inc., Chicago, IL). Statistical significance was determined at p-values below 0.05.

3. RESULTS AND DISCUSSION

3.1 Generation of PG-loaded SMEDDS dataset

Data visualizations of 30 experimental PG-loaded SMEDDS formulations in terms of DS, PDI, ZP, and %DL are illustrated in Figure 1. The DS of each formulation ranged from 166.1 to 312.3 nm. The appropriate DS of PG-loaded SMEDDS should be less than 300 nm to facilitate delivery into the target sites, while the PDI, which refers to the

droplet size distribution, should be less than 0.4. The PDI serves as an indicator of the colloidal solution of nanoparticles, describing the width or spread of the DS distribution. A high PDI value can also indicate droplet aggregation or coalescence resulting from variations in droplet sizes, both small and large, thereby affecting the consistency and stability of the particles (Clayton et al., 2016). In this study, the PDI ranged from 0.17 to 0.64. The ZP of PG-loaded SMEDDS should be greater than +30 mV or less than -30 mV to prevent droplet aggregation of colloidal systems, which can lead to unstable DS. In this study, the ZP ranged from -22.1 to -45.33 mV (Jaiswal et al., 2014; Suriyaamporn et al., 2022). The %DL in this study represented the amount of drug that could be entrapped in SMEDDS compared with the initial drug loading. The highest %DL observed in this study ranged from 16.25% to 31.20%.

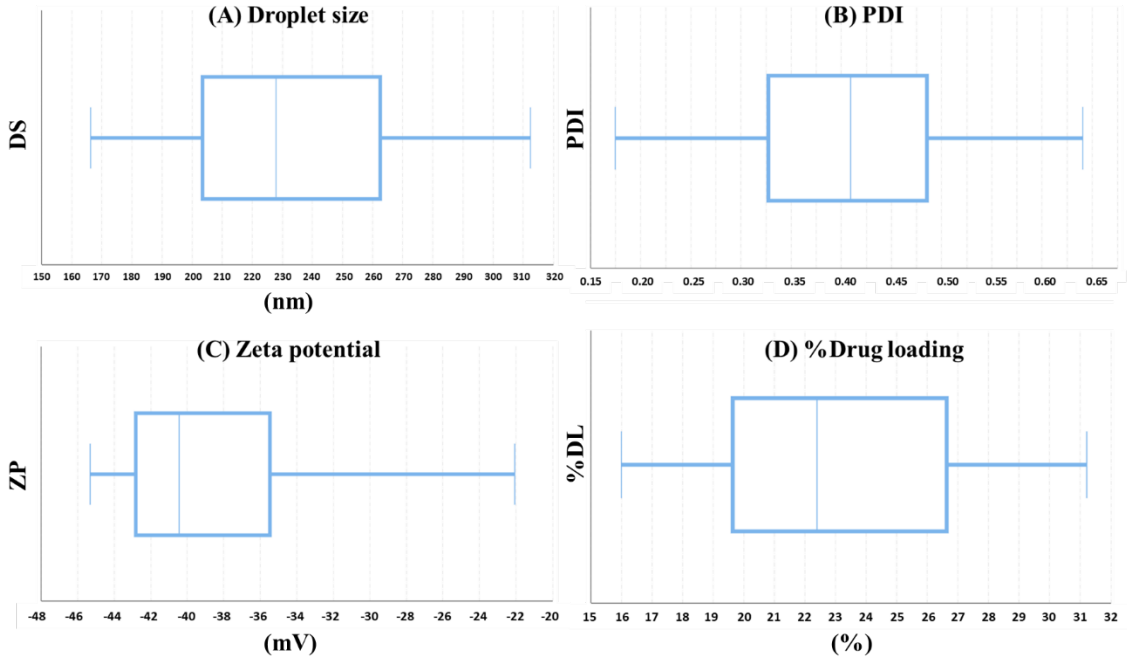

Figure 1. The data visualizations (box plot graphs) of (A) DS, (B) PDI, (C) ZP, and (D) %DL from the experimental study, illustrated the individual and distribution values such as the median, upper limit, and lower limit

For the data preprocessing step, the outliers were removed, and values for DS and PDI exceeding 300 nm and 0.4, respectively, were eliminated. ZP values > -30 mV were also removed from the dataset. Finally, the dataset was normalized for data analysis to generate a prediction model. The total number of data points after the preprocessing step was 20.

3.2 Prediction model of PG-loaded SMEDDS formulation using machine learning algorithms

The results in Table 2 present the performance of various machine learning algorithms in predicting outcomes for PG-loaded SMEDDS formulations. The results evaluated included RMSE and R^2, which provided insights into the accuracy and goodness-of-fit of each algorithm. Linear regression (LR) emerged as the top-performing algorithm across all assessed parameters, exhibiting the lowest RMSE values and the highest R^2 values compared to the other algorithms. This suggested that a linear relationship existed between the input data and the predicted outcomes. The observed trends in the dataset indicated a predominantly linear correlation, where changes in individual components had a proportional impact on the outcome in the context of linear regression (Janairo et al., 2021). PR displayed competitive results, particularly in predicting %DL but fell short in terms of overall performance compared to linear regression. SVR and K-NN demonstrated comparable performances, with both algorithms exhibiting reasonable accuracy across the evaluated parameters. GPR and NN models showed less favorable results, indicating their limitations in capturing the underlying patterns in the dataset.

Table 2. The performance of machine learning algorithm for generated prediction model of PG-loaded SMEDDS formulations

ML algorithms	DS		PDI		ZP		%DL	
	RMSE	R^2	RMSE	R^2	RMSE	R^2	RMSE	R^2
LR	0.08	0.64	36.72	0.48	4.926	0.59	2.77	0.81
PR	0.08	0.48	118.80	0.34	246.21	0.19	15.66	0.63
SVR	0.09	0.50	40.65	0.34	5.172	0.35	3.11	0.72
K-NN	0.08	0.48	38.47	0.37	4.73	0.59	2.99	0.74
GPR	0.28	0.46	140.42	0.50	22.96	0.19	12.72	0.35
NN	0.08	0.48	36.86	0.43	5.50	0.54	2.51	0.78

The correlation matrix presented in Table 3 provides valuable insights into the relationships between input data (eugenol, Labrasol®, and ethanol) and output data (DS, PDI, ZP, and %DL) in the context of PG-loaded SMEDDS formulations. Correlation coefficients ranged from -1 to 1, with positive values indicating a positive correlation, negative values indicating a negative correlation, and 0 indicating no correlation (Rodríguez-Pérez and Bajorath, 2021). The DS and PDI showed moderate positive correlations of 0.472 and 0.595 with Labrasol®. This suggested that as the amount of Labrasol® increased, there was a corresponding increase in DS and PDI. The PDI exhibited a moderate negative correlation of -0.430 with eugenol, implying that higher concentrations of eugenol may be associated with a decrease in PDI. Regarding the ZP result, a moderate negative correlation of -0.302 existed with ethanol, indicating that higher ethanol concentrations are associated with decreases in ZP. In %DL, a strong negative correlation of -0.645 existed between ethanol and %DL. A moderate correlation of 0.410 was found between eugenol concentration and %DL, suggesting that higher concentrations of ethanol and lower concentrations of eugenol were associated with a notable decrease in %DL.

These correlation coefficients provided initial insights into the relationships within the dataset. The correlations of eugenol, Labrasol®, and ethanol played a significant role in the physical properties of PG-loaded SMEDDS. The surfactant and co-surfactant were important components in reducing the energy surface tension between oil and water to form droplets (Gurram et al., 2015). The ZP is mostly influenced by eugenol and surfactant due to the high negative charge from eugenol and the uncharged nature of ethanol (Xue et al., 2019). This countercharge is very important for the ZP. The entrapping efficiency of the drug in the SMEDDS formulation is mostly influenced by the concentrations of eugenol and ethanol. The PG has a high log P value of 3.9; therefore, it easily dissolves in oil, following the principle of 'like dissolves like' (Akula et al., 2014).

Table 3. The correlation matrix of input and output data

Attributes	Eugenol	Labrasol	Ethanol	DP	PDI	ZP	%DL*
Eugenol	1.0	-0.058	-0.448	-0.037	-0.430	-0.200	0.410
Labrasol	-0.058	1.0	-0306	0.472	0.595	0.143	-0.174
Ethanol	-0.448	-0.306	1.0	-0.225	-0.253	-0.302	-0.645
DP	-0.037	0.472	-0.225	1.0	0.615	0.372	0.289
PDI	-0.430	0.595	-0.253	0.615	1.0	0.362	-0.062
ZP	-0.200	0.143	-0.302	0.372	0.362	1.0	0.452
%DL*	0.410	-0.174	-0.645	0.289	-0.062	0.452	1.0

Note: *%DL indicated to %drug loading

Table 4. Experimental results and model prediction of DS, PDI, ZP and %DL with RMSE

Formulations	DS		PDI		ZP		%DL	
	Actual	Predict	Actual	Predict	Actual	Predict	Actual	Predict
T1	256.47	265.47	0.43	0.62	-34.09	-33.06	21.32	22.82
T2	250.87	260.88	0.50	0.56	-36.87	-36.65	19.34	18.28
T3	200.50	219.59	0.40	0.30	-45.34	-43.86	17.00	17.59
T4	190.30	203.55	0.24	0.23	-43.92	-43.88	24.32	21.79
T5	294.50	267.77	0.39	0.45	-34.53	-38.52	27.45	25.08
RMSE	0.103		16.35		1.960		1.774	

Note: T1-T5 indicated formulations 1 to 5 in the unseen testing dataset

To implement and assess the prediction model, five new randomly unseen testing datasets of PG-loaded SMEDDS were formulated and measured. The RMSE values are reported in Table 4, with results showing that the linear regression prediction model, generated by machine learning, demonstrated high accuracy, as evidenced by the lowest RMSE values. However, the accuracy of predicting PDI showed a slightly high RMSE value; therefore, concerns may arise regarding the prediction of PDI when using this model.

Our prediction model forecasted a DS < 300 nm, ZP < -30, and the highest %DL. However, concerns should be raised regarding the accuracy of predicting PDI. Our prediction model can be applied to formulate SMEDDS-based formulations with appropriate DS, PDI, ZP, and %DL in pharmaceutical technology and practical applications.

3.3 Characterization of predicted PG-loaded SMEDDS formulations

Results in Table 5 report the physicochemical properties of predicted PG-loaded SMEDDS formulations including SME time, cloud point, pH, and viscosity. For SME time, representing the time taken for self-micro emulsification, values ranged from 29.4±1.2 s to 39.3±2.3 s, with lower SME times indicating faster self-micro emulsification (Anand et al., 2019). The cloud point indicates the temperature at which the formulation becomes turbid or phase separates. Cloud point values varied from 65.7±0.3 °C to 71.3±1.3 °C, suggesting that all formulations were sensitive to high temperatures. The cloud point should be above 37 °C to maintain the stability of the formulation when applied at body temperature (Jaiswal et al., 2014). The pH values ranged from 5.53±0.32 to 6.10±0.56. The formulations maintained a slightly acidic pH, which might be suitable for oral or transdermal applications (Akula et al., 2014; van Staden et al., 2020). Lastly, viscosity values ranged from 10.32±1.43 cP to 14.23±0.32 cP. All formulations showed lower viscosity, indicating a more liquid formulation that might influence ease of administration and quick emulsification (Emad et al., 2023). The SME time, cloud point, pH, and viscosity showed no significant differences. Overall, these physical properties provided important insights into the performance and characteristics of the PG-loaded SMEDDS formulations.

Table 5. The characterization of predicted PG-loaded SMEDDS formulations

Formulations	SME time (s)	Cloud point (°C)	pH	Viscosity (cP)
T1	30.0±5.4	65.7±0.3	5.98±0.13	14.23±0.32
T2	32.3±1.3	67.4±0.9	6.01±0.23	12.43±2.24
T3	39.3±2.3	70.3±1.2	5.93±0.32	10.32±1.43
T4	30.5±2.2	69.3±2.3	6.10±.0.56	13.45±1.76
T5	29.4±1.2	71.3±1.3	5.53±0.32	12.98±0.65

4. CONCLUSION

This study detailed the utilization of machine learning algorithms to construct a predictive model for PG-loaded SMEDDS formulations. Our method showcased that the linear regression algorithm outperformed other comparative machine learning algorithms in accurately predicting DS, PDI, ZP, and %DL based on experimental conditions. The DS, PDI, ZP, and %DL were acceptable criteria for formulation development. In contrast to traditional approaches, this method demanded fewer resources and less time, thereby expediting the production process. Consequently, AI facilitated the prediction of diverse characteristics and delved into the intricate relationships governing the behavior of nanomaterials. The physical properties of predicted PG-loaded SMEDDS such as SME time, cloud point, pH, and viscosity demonstrated suitable performance and characteristics.

Our research findings presented an optimal predictive AI model for determining PG-loaded SMEDDS formulations. This AI model can adjust the components of the PG-SMEDDS formulation in real-time to predict DS, PDI, ZP, and %DL before formulation in real situations, reducing both time and cost. This research established fundamental knowledge regarding AI applications in pharmaceutical research and development. The incorporation of advanced tools like AI holds great promise in advancing the field of nanomedicine, generating novel insights and influencing future developments. In the future, predictive AI models will accurately predict and formulate drug formulations with desired properties, leading to personalized drugs for patients.

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