*Journal of Biological Regulators and Homeostatic Agents*2026, 40(3), 127.
https://doi.org/10.65746/jbrha127

Article

Innovative drug release forecasting using RNN-LSTM deep learning algorithms

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CITATION

Babylatha M, Rajan C, Geetha K. Innovative drug release forecasting using RNN-LSTM deep learning algorithms. Journal of Biological Regulators and Homeostatic Agents.2026; 40(3): 127. https://doi.org/10.65746/jbrha127

ARTICLE INFO

Received: 8 June 2026
Revised: 15 June 2026
Accepted: 14 July 2026
Available online: 11 August 2026

Abstract: The drug delivery acceleration is done by employing the deep learning (DL) process through huge data recognition for probable drug target discovery, physicochemical properties prediction, drug design optimization, and probable toxicity estimation directed to quicker and more capable expansion procedures than conventional schemes. According to the in-vitro data, systems have been designed for drug release patterns inside the human body. Multifarious data associated with the tablets, excipients, and mechanized parameters, frequently previous to general execution in-vitro experiments, fundamentally with the help of an artificial intelligence (AI) scheme to form and forecast how a medicine is liberated from its mover over time. In this paper, for the drug release uniqueness evaluation, dissolution, hardness, and disintegration parameters are discovered efficiently by applying an efficient DL system. The non-negative Matrix Factorization (NMF)-based RNN-LSTM (Recurrent Neural Network-Long Short-Term Memory) method is presented in this work for the drug's release profiles efficiently through multifarious chronological dynamics recognition of how a tablet could be released from its deliverance scheme, frequently characterized as a data point's series. The performance of the proposed DL system was evaluated using Accuracy, Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), and the coefficient of determination (R^2) to assess the prediction of drug hardness, disintegration time, and dissolution profiles. Experimental results of the presented scheme have demonstrated that the probability of a DL-based AI method has solved nonlinear time-series discovery issues in drug product growth.

Keywords: drug release prediction; pharmaceutical formulation; artificial intelligence; deep learning; RNN-LSTM

1. Introduction

DL systems can be employed as a subsystem of machine learning (ML), and they have utilized methods that were inspired by the construction and human brain' processes, and they are known as neural networks (NNs). DL-based NNs have been varied from the conventional NNs depending on their depth, which utilized various hidden layers during which data could be passed, and also several neurons in hidden layers. The NNs are exploited as the backbone of DL methods. In recent decades, deep learning-based neural networks have been utilized in the drug formulation processes [1,2]. Frequently, DL schemes are applied in recent years as a constructive tool to optimize and discover preferred effective drug profiles in a Pharma 4.0 perception. Compared to the trial plan, the NN merit can be the prospect of a

concurrent model of huge variables. Besides, difficult relationships are established, flanked by independent and dependent variables [3–6].

For the pharmaceutical formulation, the DL system has leveraged huge, multi-dimensional drug datasets containing polymer assets, medicine particles, element dimensions, and ecological situations, which could be frequently concerned in drug release examinations. In several drug prediction schemes, DL can play a vital role. Such schemes are peptide synthesis, monitoring of tablets, fable-based essential viewing, pharmacophore modeling, toxicity forecasting, quantitative structure–activity relationship (QSAR), drug moving, physiochemical behaviors, and polypharmacology. Research workers discover how the various pharmaceutical formulation parameters can affect profiles of tablet release, facilitating the optimization process before the substantial combination [7–9]. Drug development procedures will be hastened through the DL system by discovering capable pharmaceutical formulations and reducing the requirement for time-consuming trial procedures. Key factors could be discovered to manipulate the drug release kinetics with many-sided in-vitro dataset interpretation exploiting the DL model [10–13].

Numerous pharmaceutical formulations were constructed with the help of deep learning by drug release profile prediction [14,15]. The drug release profile prediction is needed during the process of drug development to recognize possible problems with pharmaceutical formulation reliability. According to the individual patient points, drug release is modified through their distinctive release profiles. By employing the DL system, drug release profiles can be predicted, in which data is analyzed from pharmaceutical formulations and forecasts how rapidly a medicine can be delivered from a definite release scheme, such as a drug or scrap, over time, permitting examiners to optimize drug release features before substantial combination and examining in the experimental lab; this could be attained by influencing the DL capability for multifaceted data pattern prediction in huge datasets associated with physiochemical properties, parameters of pharmaceutical formulation, and drug delivery profiles [16–19]. Deep learning models can analyze various data points like disintegration time, drug concentration, hardness, dissolution time, molecule size, ecological situations, and excipient properties during the process of drug delivery profile prediction [20,21].

Dissolution time, hardness, friability, and disintegration time can be vital parameters in drug release profile assessment, in which dissolution will estimate the rate at which a tablet melts in a fluid standard, whereas friability, hardness, and disintegration can estimate the substantial reliability of the drug, making sure it has broken properly to assist tablet delivery in the patient's body; fundamentally, enhanced disintegration could be vital for medicine inclusion and finest dissolution [22]. More precise predictions have been given by DL systems than conventional schemes such as least regression analysis owing to their capability for capturing difficult interactions. Costs and time reduction are done through early prediction of drug release features during the process of drug development [23]. Thus, more information about drug release profiles exploiting the DL system has directed the drug research workers to find efficient pharmaceutical formulations with chosen drug release factors. In this paper, NMF-based RNN-LSTM is presented to assess and predict drug release profiles by estimating drug hardness, disintegration time,

and drug dissolution rate, in which data noise could be eliminated and feature engineering is accomplished with the help of an efficient feature extraction method, and model training and prediction are accomplished.

2. Related works

For colonic drug release, the ML scheme was leveraged to obtain improved throughput and drug properties assortment tools, and openly reachable experimental data has been applied for drug five-aminoalicylic acid prediction from polysaccharide-based outside layers in virtual person, louse, and dog colonic conditions. The polysaccharides were differentiated through Raman spectra for input as characteristics of machine learning. In this study, schemes could be authenticated on eight hidden drug delivery kinetics from novel polysaccharide out-layers [1]. The encapsulated tablet delivery has been examined in [2] from poly lactic-co-glycolic micro-nano-molecules. For the study assessment, experimental data was gathered from about fifty journals that could be examined with the help of ML schemes such as principal component analysis (PCA), Gaussian process regression, linear regression (LR), and ANNs. In this examination, the weight of the medicine molecule, drug dissolution, element size, and the delivery matrix or setting was estimated on drug delivery kinetics [2]. A combined machine learning scheme was applied for the silver sulfadiazine's release profiles discovery from temperature-approachable hydrogels according to the in-vitro data. In this examination, variations of hydrogel formulations and cellulose percentages, medicine attentiveness, and hotness were discovered. For the evaluation process, six machine learning methods have been utilized, such as LR, random forest (RF), Gaussian regressor, support vector machine (SVM), and kernel ridge for the drug-release data discovery [3]. Depending on the focal point signal, the smart drug delivery scheme has recognized the ON and OFF direction of drug release processes and was built through polymer-based tablets. The microstructure of the polymer can be modified reversibly while the situation of smart polymer modifications, in which the hydrophilic condition is changed to the hydrophobic condition. Consequently, a drug release scheme reacting to various stimulus signals has been built. For the second-class categorization, SVM was utilized in [5] according to the arithmetical knowledge hypothesis [4]. A technique was presented depending on the transportable near-infrared (NIR) spectrometer that was incorporated with the ML scheme for the *sinomenine* hydrochloride (SH) sustained delivery tablets' solubility activities prediction. In the study, 78 tablet groups have been constructed with various solubility activities. PCA, isolation forest, and *Mahalanobis* detachment were estimated to discover outliers. In this study, the solubility kinetics prediction models were developed by applying the partial least squares regression (PLSR), Gaussian process regression (GPR), and convolutional neural network (CNN) algorithms [5].

A new method was introduced in [6] for cancer drug release enhancement. ML algorithms have been combined in this study to reform treatment accuracy and effectiveness. The nanoparticles were examined by employing the Levenberg–Marquardt neural network (LM-NN). Drug hardness and disintegration time were assessed during the examination of the drug release system. For the model's

presentation and comparison process, DL, SVM, decision trees (DTs), ANN, multiple linear regression (MLR), and RF are evaluated and compared. By employing the scikit-learn package, the models have been trained. The ANN has been constructed with an input layer, a hidden layer with two hundred and fifty-six neurons, and an output layer of a neural network. The ReLU was applied as an establishment process in the hidden layers, and with a learning rate of 0.001, the Adam optimizer has been exploited. A linear kernel for the support vector machine model is exploited, while a kernel of radial basis function has been applied for recurrent neural networks [7]. A real-time technique was utilized in [8] to discover the CQAs (Critical Quality Attributes) in a Hot Melt Extrusion (HME) procedure with the help of ML schemes. In processing situations, the automatic and tablet solubility properties have been discovered to differ considerably with alters, and real-time machine learning schemes were highlighted for the drug product properties prediction to monitor and optimize the drug release profiles. Nonlinear ML schemes were employed for computation and comparison, such as K-Nearest Neighbors (KNN), RF, and Recursive Feature Elimination with RF (RFE-RF). Various ML principles have been provided in [9] to evaluate PDDS (polymeric drug delivery schemes) drug delivery activities. Besides, issues are discovered that relate to machine learning-based drug release forecasts, and modern solutions are presented while investigating future viewpoints. In the study, the ANN scheme's importance was analyzed in machine learning-based PDDS drug release kinetics forecasts, exceeding both customary and other ML-based methods that were examined. An alternative ML scheme was presented for the disintegration time optimization according to an extensive assortment of ML schemes by the H2O Auto-ML condition [10].

3. Proposed methodology

In this paper, an effective DL system is presented to estimate and predict the drug release profiles with more prediction accuracy. In the study, experimental data was gathered on drug release profiles from various pharmaceutical formulations. Initially, noisy data can be cleansed from the gathered data by applying the multilinear regression (MLR) method, and data could be converted into an appropriate system for the DL system. Subsequently, pertinent features are extracted with the help of NMF structure, in which, outside region, polymer properties, and particle size delivery might be extracted from the collected pharmaceutical data for the DL system's prediction performance improvement. According to the extracted features, the RNN-LSTM deep learning system can be trained. During the training process, related input features are learned with the equivalent drug release profiles. Once the DL has been trained, the drug release profile of new pharmaceutical formulations will be predicted depending on their extracted features. In this work, hardness, disintegration time, and dissolution can be estimated through evaluation criteria to discover the drug release profiles efficiently. The presented drug release discovery contains the following phases:

3.1. Data acquisition

For drug release examination, pharmaceutical data is gathered on formulation attributes such as API (active pharmaceutical ingredient), excipients, etc.; investigational situations like medium, hotness, etc.; and pertinent factors such as hardness, dissolution profiles, disintegration time, rates of drug delivery, and dissolution kinetics. Here, experimental data is collected from a database published in Web of Science that has reported in-vitro drug release examinations. Three kinds of drug release factors have been assessed for the experimental study: (i) drug hardness—the drug's mechanical assets could be examined to assess the hardness of the mechanical properties of the drug; (ii) drug disintegration time—the time in use for the drug to disintegrate entirely; (iii) dissolution profiles—estimates how the drug solubility is done over time. Sharing of particle sizes in the pharmaceutical formulation is recognized for hardness assessment. To analyze disintegration time and dissolution of the drug, the data about pH, temperature, category, and ionic power of the drug are gathered. In the process of dissolution estimation, quantity, velocity, and category (like basket or paddle) can be analyzed. The training pharmaceutical data has been exploited to train the DL, training and validation data was employed to regularize the optimization of deep learning, and finally, test data could be applied for novel pharmaceutical dataset's performance checking that might not be exploited for the model training. In this paper, effectively extracted most relevant features are applied to train the RNN-LSTM system for drug release prediction.

3.2. Data cleansing

Once the experimental pharmaceutical data is collected, the process of data cleansing will be achieved via the MLR procedure as data quality improvement strategy by converting unstructured pharmaceutical data into structured data via eliminating the unnecessary and inconsistent records within the collected data set. This collected data may contain some errors, missing data, and abnormal data, which are far away from feasible pharmaceutical measurement. Hence, these errors can be minimized by using the MLR procedure to get the smoothed and consistent data.

In order to increase the reproducibility of the pre-processing step, the abnormal pharmaceutical data screening criteria have been explicitly stated prior to the modeling of the MLR model. The standardized residual from the regression model was used as an approach for finding the abnormal observation. The data with the absolute value of standardized residual larger than 3.0 (|Standardized Residual| >3) will be regarded as outlier. Moreover, Cook's Distance is used as a tool for identifying influential observation, where samples with Cook's Distance larger than 1 are regarded as influential.

In terms of data smoothing, missing data less than 5% of the total data set were imputed by calculating the median of that particular data variable. The continuous pharmaceutical data of hardness, disintegration time, and dissolution rate were further normalized using the Z-score normalization technique. The obtained MLR model was employed for predicting the expected data with minimized prediction error using the least-squares technique. The data points which showed small

discrepancies (less than ±3 standard deviation) were kept and smoothed through regression predictions. In this way, noise in the experimental data was considerably reduced without affecting the intrinsic nature of the pharmaceutical data set.

The experimental data was smoothed with the help of the MLR system initially. The steps of the data cleansing using MLR have been illustrated in **Figure 1**. In this data cleansing scheme, the relationship was modeled, flanked by two or more independent data or dependent data attributes, through a straight-line fitting process. By employing the predictor functions, the relationships have been modeled, in which indefinite model parameters were evaluated from the experimental pharmaceutical data. More than two pharmaceutical data attributes are fitted to discover the best line, and consequently, data attributes are exploited for other predictions. The following Algorithm 1 is applied for the data cleansing process:

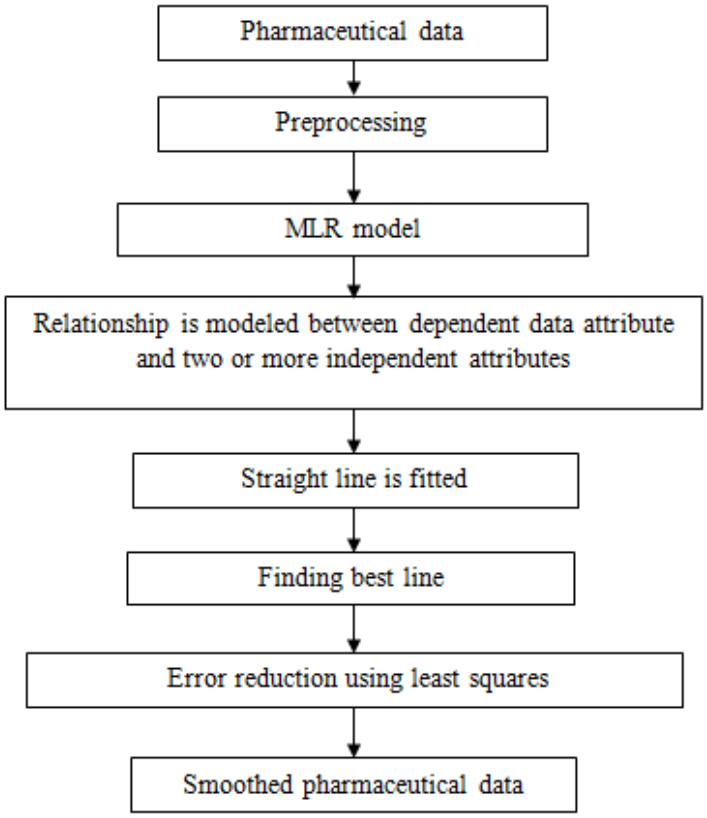

Figure 1. Steps of data cleansing using MLR.

3.3. Feature engineering

Pertinent characteristics are discovered and extracted from the preprocessed data for the drug release examination to recognize and forecast drug release kinetics using the NMF method. The features could be formulation factors, release factors, and physicochemical properties. Features for the pharmaceutical formulation factors associated with the drug release scheme, like category of polymer, size of particle or molecule, and excipients that have controlled the drug delivery. Physiochemical properties are extracted, such as permeability, solubility, and molecular mass, and these are employed as features. For the drug release factors, dissolution, hardness,

and disintegration time-based features can be analyzed and extracted. Through these features of recognition and extraction, pharmaceutical research workers will realize how the various kinetics (excipients, formulation, and developing procedure) have affected drug delivery. This kind of NMF-based feature extraction method is used to forecast the drug's in-vivo presentation according to the in-vitro drug release profiles. Most important features analysis is used to get improved optimization of pharmaceutical formulations for the preferred drug release profiles attainment.

$$y_i = \beta_0 + \beta_1 x_{i1} +, \dots, \beta_p x_{ip} + \varepsilon_i \; for \; i = 1,2, \dots, n \tag{1}$$

$$S = arg \min_{\vec{\beta}} \sum_{i=1}^{n} (\vec{\beta}.\vec{x} - y_i)^2 \tag{2}$$

In this approach, the decomposition rank *(r) w*as considered as the main hyperparameter as it determines the number of latent features being extracted from the pharmaceutical data set. The search for the optimal value of the decomposition rank was performed via the grid-search approach within the interval of ranks [5] using the training data set. The most suitable decomposition rank was chosen in terms of minimal reconstruction error and prediction accuracy using RNN-LSTM approach. As a result of this experiment, *r* = 15 was determined to be the best choice in terms of the trade-off between the quality of feature extraction, efficiency, and prediction accuracy. The lower rank led to information loss due to insufficient latent feature representation, while the higher one implied redundant features without any significant increase in the accuracy of predictions.

Algorithm 1 MLR

Input: Pharmaceutical data, dependent data attribute, and independent data attributes

Output: Preprocessed data

Step 1: To read pharmaceutical data

Step 2: To initialize dependent data attribute y and two or more independent data attributes $\{x_1, x_2, \dots, x_n\}$.The independent attribute x's each value has been linked to a dependent data attribute y value.

Step 3: To fit the straight line for relationships modeling among two or more predictor variables and a reaction variables, we used the following Equation (1)

In Equation (1), response variable is represented by y, predictor variable is denoted by the symbol of x, error variable is denoted by ε that is utilized to model the relationship, and the noise could be added to the linear relationship among the independent and data attributes, and β can be the regression.

Step 4: To apply the least squares scheme to estimate error among the definite line unraveling the pharmaceutical data and compute line reduction by employing the following Equation (2).

Where$\vec{\beta} = \{\beta_0, \beta_{1,\dots,}\beta_p\}$ and $\vec{x} = \{x_1, x_2, \dots, x_p\}$

Step 5: Finally, the given experimental data has been smoothed by applying an error-lessening

In the NMF method, a high-dimensional data matrix can be decomposed into two lower-dimensional matrices W and H to extract the features during the examination of drug release profiles, in which a unique matrix (V) is identical to the

product of $W\ and\ H(V \approx WH)$ with non-negative components; essential data patterns and associations are exposed in the pharmaceutical data. Hidden characteristics are discovered by the NMF method in experimental data that has been complicated to distinguish with conventional schemes. Recognition is simplified, and prediction process effectiveness was enhanced through data dimensionality reduction by NMF. Enhanced interpretable consequences are provided by the NMF's non-negative restraint since the parameters ($W\ and\ H$) have characterized the fundamental elements in the experimental pharmaceutical data in a method that could be very simple to recognize.

In NMF, a non-negative matrix $V \in \mathbb{R}^{+}_{K\times N}$ has been decomposed into two matrices such as$W \in \mathbb{R}^{+}_{K\times R}$and $H \in \mathbb{R}^{+}_{R\times N}$, and it is estimated as:

$$V \approx WH \tag{3}$$

The matrices $W\ and\ H$ are computed using the following Equation (4):

$$\begin{cases} W = arg\min\limits_{W} D(V|WH) \quad for\ fixed\ H \\ H = arg\min\limits_{H} D(V|WH) \quad for\ fixed\ W \end{cases} \tag{4}$$

In Equation (4), the distance process among V and WH is represented by $D(V|WH)$. The multiplicative revise condition is optimized with the help of the distance process and is given by:

$$W \leftarrow W \otimes \frac{\left[\frac{V}{WH}\right]H^T}{1_{K\times N}H^T} \tag{5}$$

$$H \leftarrow H \otimes \frac{\left[\frac{V}{WH}\right]W^T}{1_{K\times N}W^T} \tag{6}$$

While the Kullback–Leibler divergence (KLD) has been exploited as the distance process, wherever a $K \times N$matrix of 1s is represented by $1_{K\times N}$, and is computed as:

$$W \leftarrow W \otimes \frac{VH^T}{WHH^T} \tag{7}$$

$$H \leftarrow H \otimes \frac{VW^T}{WHW^T} \tag{8}$$

In Equations (7) and (8), Hadamard (element-wise) product and division can be represented by $\otimes$ and the divisions.

3.4. Deep learning model training and prediction

According to the extracted features, the RNN-LSTM deep learning model is trained to predict drug release kinetics. The deep learning model can utilize extracted features as input, like pharmaceutical formulation factors, physiochemical properties, and drug release factors (hardness, disintegration time, and dissolution). In this study,

the RNN-LSTM model has been trained on a pharmaceutical dataset with recognized drug delivery kinetics. The aim of this DL training process could be the finest factor discovery for the unidentified drug release profiles prediction. Once the RNN-LSTM model's training process is completed, novel pharmaceutical formulation drug release profiles are predicted efficiently with the help of the trained RNN-LSTM system for drug release discovery and formulation optimization.

RNNs are applied for the drug release profiles discovery depending on the NMF-extracted features from several formulations. LSTMs can be appropriated to predict drug delivery kinetics since they have modeled time-dependent experimental data, and chronological reliance is discovered that might be vital to recognize and forecast the drug release factors. The RNN model was established in this work as an influential tool to examine different categories of time series-based drug data. During the drug release, the time-series estimations of medicine attentiveness are accomplished with RNN, which has made an LSTM model an influential tool for drug release prediction. RNN deep learning contains a memory element that is used to maintain data from preceding inputs that could be necessary to predict future drug release activities according to the drug release process' history. This historical pharmaceutical data recognition by RNN-LSTM can discover future values for drug release.

This RNN-LSTM model has an RNN layer (64 hidden nodes), which is followed by the LSTM layer (128 memory nodes) and the fully connected output layer to predict the drug release properties. The training of the model was performed with the Adam optimizer about 0.001 learning rate and batch size of 32 for 100 training epochs. The ReLU activation function was used in the hidden layers while the linear activation was used in the output layer to make the predictions. Early stopping was utilized to ensure better generalization and to avoid overfitting of the model.

3.4.1. RNN model training

The RNN training has been illustrated in **Figure2**. For the RNN model training, the following steps are applied for drug release kinetics prediction:

Step 1: To execute the onward pass by applying the hidden states or weights.

Step 2: To estimate the loss function with the help of the known experimental and predicted values, it is computed as:

$$G(\omega, b) = \frac{1}{N}\sum_{k=1}^{N} l\left(\hat{y}^k, y^k\right)^2 \tag{9}$$

In Equation (9), the bias vector is represented by the symbol of b, the matrix of weight is denoted by ω,$\hat{y}^k$ indicates the predicted value, the number of extracted features (inputs) is represented by N, l has represented the loss value flanked by the experimental and predicted values, and the experimental value is denoted by sy^k. The cost function G will be exploited for the number of loss discoveries that occur after each iteration process.

Step 3: To execute the backward pass for the essential inclines attainment to decrease the loss function and update the weights of the neural network.

Step 4: To apply attained inclines and repeat steps (steps 1 and 2) for the weights of neural network updates.

Step 5: Repeat steps 1 to 4 until an established loss threshold can be attained.

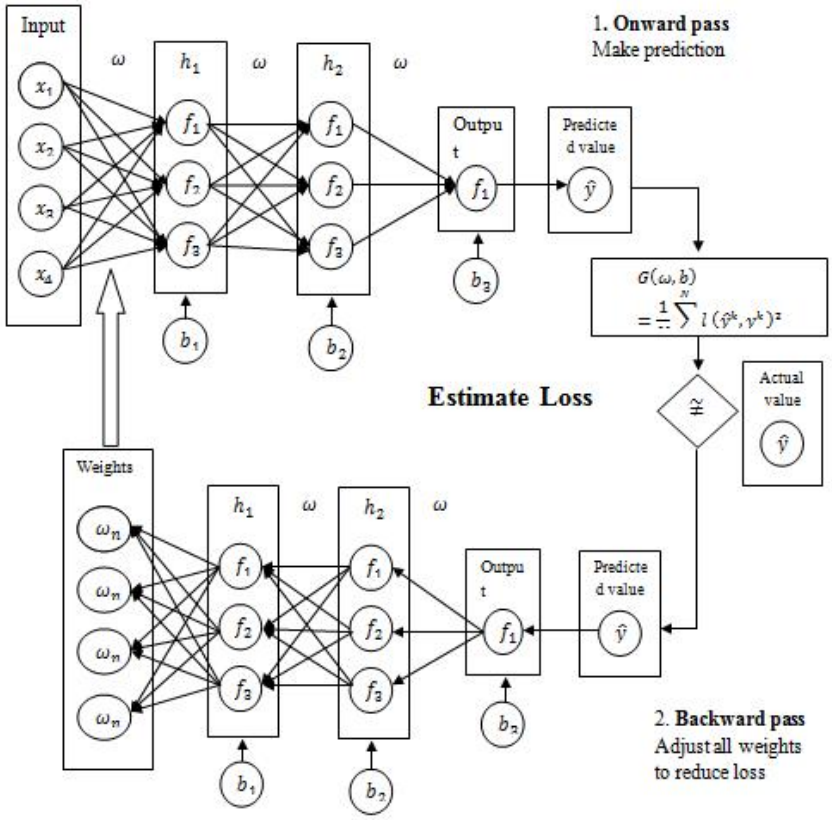

Figure 2. Overall training of RNN scheme.

3.4.2. LSTM model training

In the training process, extracted features from drug delivery data are configured as a series and provided to the network of the LSTM deep learning model as input. Gates are utilized in the LSTM model to direct the information flow via the network, and it enables it to consider pertinent data from preceding time phases as not remembering unrelated features. The LSTM method has been trained for pattern learning within the experimental data, regulating its interior factors to precisely forecast the drug attentiveness of the next time phase according to the preceding series. LSTM elements could be utilized in RNN models for data pattern assessment problems in the chronological data over deviating time steps. In a layer module of an LSTM layer, memory elements are handled by the memory cells, in which an input and output gate, a forgetting gate, and a window association is exploited. For the controlling of input and hidden states, connected weights can be analogous to those that modify throughout training. For the LSTM element, activation functions have been described by applying the following Equations (10)–(13) to predict drug release profiles effectively.

The input gate vector $I_t$of the LSTM model is estimated using the following Equation (10):

$$I_t = \sigma\left(\omega^{(i)} p_t + A^{(i)} h_{t-1} + b^{(i)}\right) \quad (10)$$

In Equation (10), p_t represents the input vector at time phase t, weights of the input matrix-to-hidden matrix are denoted by the symbol of ω, weights of the hidden matrix-to-hidden matrix are represented by A-, h_{t-1} denotes the preceding hidden condition vector, andBias vector is denoted by b.

Subsequently, the forget gate vector of the LSTM model can be calculated with the help of Equation (11):

$$F_t = \sigma\left(\omega^{(F)} p_t + A^{(F)} h_{t-1} + b^{(F)}\right) \quad (11)$$

The output gate vector in LSTM for the training process is estimated as:

$$O_t = \sigma\left(\omega^{(O)} p_t + A^{(O)} h_{t-1} + b^{(O)}\right) \quad (12)$$

State vector of memory cell in deep learning of LSTM has been estimated using the following Equation (13):

$$C_t = i_t \odot a_t + F_t \odot C_{t-1} \quad (13)$$

Where,

$$a_t = \tanh\left(\omega^{(a)} p_t + A^{(a)} h_{t-1} + b^{(a)}\right) \quad (14)$$

Finally, the hidden state vector is computed in the training of LSTM for the drug release profiles prediction using the following Equation (15):

$$h_t = O_t \odot \tanh(C_t) \quad (15)$$

Thus, the RNN-LSTM deep learning model was trained with NMF-extracted features from experimental pharmaceutical data to predict drug release kinetics with more accuracy.

3.4.3. Evaluation

For the presented DL-based drug release prediction model's performance estimation and comparison with existing prediction models, the performance metrics are employed, such as Root Mean Squared Error (RMSE), correlation coefficient (R^2), and Mean Absolute Error (MAE). The RMSE has estimated the standard deviation (STD)flanked by experimental values (target) and pre-dicted values (output). It has been evaluated with the square root of the standard variations among every experimental and predicted value, and it is computed as:

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(Target_i - Output_i)^2} \quad (16)$$

The value of the correlation coefficient has represented the fraction of the variation in the dependent variables that could be knowable from the independent variables in a regression system. It can utilize 0 and 1 values, in which an accurate set is represented by the value of 1 and is given by:

$$R^2 = \frac{\sum_{i=1}^{N}(Output_i - Target)^2}{\sum_{i=1}^{N}(Target_i - Target)^2} \quad (17)$$

For the MAE estimation, the average value of variation is flanked by the target and output values. During the process of experimental variable prediction, this performance factor can give an assessment of the accuracy of the machine and deep learning methods, and it is calculated as:

$$MAE = \frac{1}{N}\sum_{i1}^{N} |Target_i - Output_i| \quad (18)$$

Finally, the prediction accuracy of the presented and existing methods is estimated as

$$Accuracy = \frac{Number\left(\left|f_i - \hat{f}_i\right| \leq 0.1 * \hat{f}\right)}{All\ Predictions} \quad (19)$$

where, predicted value can be represented by f_i and experimental values aresymbolized by $\hat{f}_i$

4. Results and discussions

In this section, the presented DL model and existing ML and DL models are evaluated and compared using drug release factors such as hardness, disintegration time, and dissolution rate in terms of accuracy, R2, MAE, and RMSE to predict drug release kinetics. The experimental dataset for pharmaceuticals was created using peer-reviewed research articles related to drug formulations and release mechanisms. Studies that provided complete data related to formulation compositions, physical and chemical properties, hardness, disintegration time, and dissolution profiles were considered. Upon exclusion of duplicate records and those records which had incomplete data, there were a total of 1248 samples of pharmaceutical formulations available in the dataset. Each record was made up of formulation characteristics (API concentration, excipient composition, particle size, polymer type, and weight of the tablet) and physical and chemical characteristics (molecular weight, LogS, XlogP3-AA, hydrogen donor and acceptor numbers, topological polar surface area), and quality control characteristics (hardness, disintegration time, and dissolution rate). The dataset was randomly divided into 70% training, 15% for each validation and testing.

The presented DL model was compared with existing prediction models such as LM-NN [6] and SVM [4]. Sample gathered pharmaceutical dataset parameters and their elements have been summarized in **Table1**. For the hardness of drug assessment, the obtained results of the presented and existing prediction schemes are provided in **Table 2**, and the drug integration time and drug dissolution have been given in **Table 3** and **Table 4**. To assess the presented and existing prediction schemes, precision matrices were utilized, such as accuracy, R^2, MAE, and RMSE, in training, validation, and testing drug release data. In general, standard total variations between experimental and predicted hardness were measured with the help

of the MAE. The total error of the deep learning and machine learning prediction is estimated through RMSE. From **Tables 2–4**, it was demonstrated that the presented DL model has taken lesser values of MAE and RMSE for hardness, disintegration time, and drug dissolution estimation compared to the existing prediction schemes [4 – 6, 8] for drug release prediction. Enhanced prediction accuracy is given by lesser values of MAE. Enhanced performance was indicated by the lesser values of RMSE.

Table 1. Examples of pharmaceutical dataset parameters and their elements.

S.No.	Parameters	Elements
1.	Quality control examinations for drug formulations	Hardness
		Disintegration time
		Dissolution
		Friability
2.	Excipients	Excipient 1Amount
		Excipient 1Amount
		…
		Excipient 56 Amount
3.	Active element's physicochemical prosperities	Hydrogen Bond Donor Count
		Hydrogen Bond Acceptor Count
		LogS
		XlogP3-AA
		Rational Bond Count
		Heavy Atom Count
		Topological Surface Area
		Molecular Weight
		Complexity
4.	Total weight of drug	Weight of drug
5.	Active element amount	Weight of active element
6.	Features of powered material composition	Tapped Density
		Bulk Density
		Hausner Ratio
		Carr's Compressibility Index
		Angle of Repose

The variation fraction is represented by R^2. From the comparison **Tables 2–4**, the presented DL-based prediction scheme has taken higher R^2 values during the estimation of drug release factors such as hardness, drug integration time, and drug dissolution than conventional prediction models. The higher values of R^2 might be nearer to the value of 1 that has recommended enhanced fit and prognostic potential. The prediction accuracy has also been estimated and compared to represent the prediction percentage that falls within a definite percentage of the experimental values. The presented NMF-based RNN-LSTM method has given more accuracy compared to the existing schemes.

Table 2. Comparison of drug hardness prediction performance with existing models.

Methods	Training data				Validation data				Test data			
	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE
LM-NN [6]	88.74	0.0784	0.0826	0.0951	85.00	0.0937	0.0881	0.1227	85.00	0.0977	0.0895	0.1268
CNN [5]	91.24	0.0721	0.0744	0.0811	87.00	0.0796	0.0767	0.1014	87.00	0.0921	0.0817	0.1299
KNN [8]	86.55	0.0799	0.0796	0.0917	84.00	0.1160	0.0853	0.1644	84.00	0.1137	0.0877	0.1784
SVM [4]	85.87	0.0789	0.0618	0.1014	82.00	0.1189	0.0791	0.1728	82.00	0.1213	0.0813	0.1935
NMF-based RNN-LSTM	97.99	0.0327	0.0992	0.0427	96.00	0.0311	0.1011	0.0376	96.00	0.0416	0.1085	0.0357

Table 3. Comparison of drug disintegration time prediction performance.

Methods	Training data				Validation data				Test data			
	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE
LM-NN [6]	87.54	0.1134	0.1215	0.1012	85.00	0.1228	0.1221	0.1278	80.00	0.1215	0.1232	0.1281
CNN [5]	88.98	0.1093	0.1199	0.1109	82.00	0.1254	0.1106	0.1201	81.00	0.1366	0.1169	0.1229
KNN [8]	84.71	0.1099	0.1134	0.1277	80.00	0.1299	0.1154	0.1316	79.00	0.1341	0.1162	0.1387
SVM [4]	81.77	0.1368	0.1034	0.1308	79.00	0.1471	0.1071	0.1488	75.00	0.1495	0.1107	0.1573
NMF-based RNN-LSTM	97.87	0.0381	0.1299	0.0364	95.00	0.0349	0.1311	0.0396	96.00	0.0384	0.1334	0.0412

Table 4. Comparison of drug dissolution prediction performance.

Methods	Training data				Validation data				Test data			
	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE	Accuracy (%)	MAE	R^2	RMSE
LM-NN	85.26	0.1124	0.1284	0.1127	84.00	0.1275	0.1284	0.1299	84.00	0.1288	0.1272	0.1296
CNN	87.99	0.1199	0.1201	0.1184	87.00	0.1312	0.1191	0.1237	87.00	0.1394	0.1174	0.1273
KNN	84.67	0.1227	0.1085	0.1311	82.00	0.1398	0.1137	0.1384	82.00	0.1357	0.1108	0.1397
SVM	83.93	0.1341	0.1011	0.1375	80.00	0.1466	0.1112	0.1399	80.00	0.1461	0.1101	0.1501
NMF-based RNN-LSTM	97.51	0.0481	0.1318	0.1008	96.00	0.0767	0.1328	0.0411	96.00	0.0436	0.1299	0.0495

The comparison results of the various prediction models shown in **Table 5** have illustrated that every model's accuracy in accurately predicting the hardness, disintegration time, and dissolution of drugs, with the presented NMF-based RNN-LSTM scheme, has attained enhanced accuracy in diagonally different metrics than other conventional schemes. The comparison results have highlighted the better-quality presentation of the presented DL model during the process of hardness, disintegration, and drug solubility than conventional schemes to analyze the drug release. The predicted values of drug hardness, disintegration time, and drug dissolution were made by presenting an NMF-based RNN-LSTM deep learning scheme for drug release prediction that has been demonstrated in **Figures 3–5** next to the experimental values within the taken pharmaceutical dataset. These comparisons have given a methodical examination of the presented deep learning-based prediction model's accuracy at the level of every sample.

Table 5. Experimental values vs predicted values.

Hardness (newton)		Disintegration time (seconds)		Dissolution rate (%)	
Experimental values	**Predicted values**	**Experimental values**	**Predicted values**	**Experimental values**	**Predicted values**
6.40	5.8	94	94.33	0	0
2.70	2.56	13	12.62	10	11
5.30	5.57	19	19.84	25	23
2.90	3.01	21	20.43	28	27
4.66	4.69	27	25.99	30	30
3.08	3.00	30	32.12	44	40
5.89	5.63	24	24.19	57	59
3.90	3.71	75	75.98	66	65
3.54	3.65	20.12	20.77	73	70
2.48	2.50	37	34.96	88	89
5.72	5.51	45	49.25	97	95

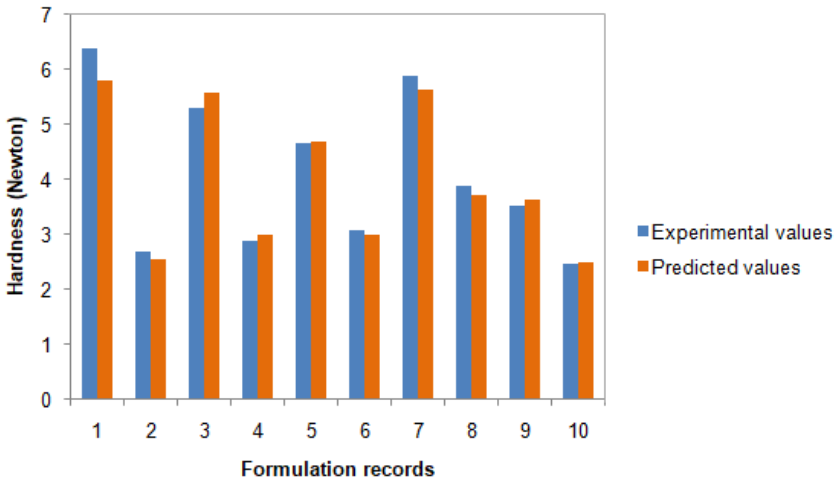

Figure 3. Predicted hardness values vs experimental values – NMF-based RNN-LSTM.

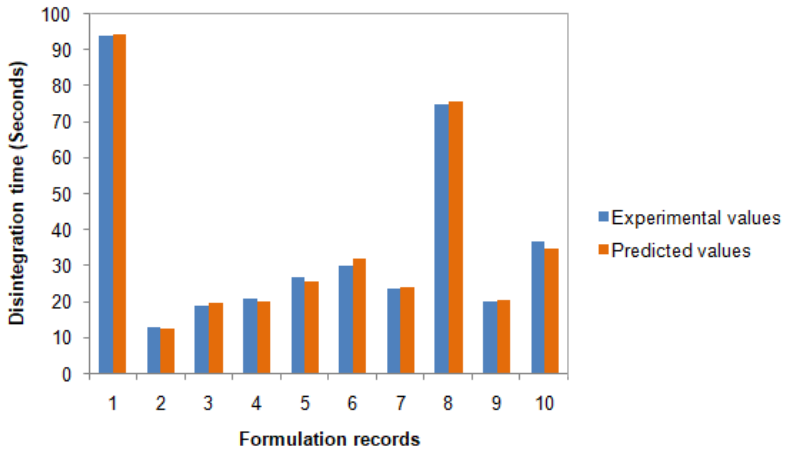

Figure 4. Predicted disintegration time values vs. experimental values - NMF-based RNN-LSTM.

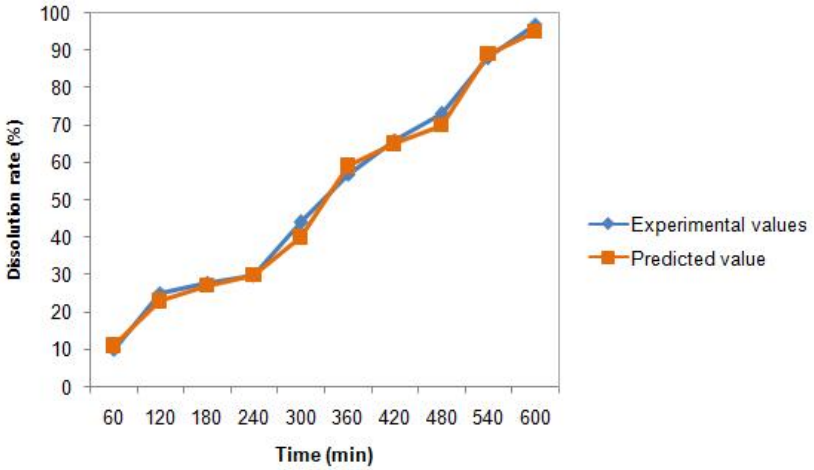

Figure 5. Predicted dissolution rate values vs. experimental values - NMF-based RNN-LSTM.

The **Table 6** indicates the contributions of each module to the overall predictive performance. It is clear from **Table 6** that the exclusion of either MLR pre-processing module or NMF feature extraction module leads to poor prediction performance since the prediction error will increase and the accuracy will be reduced. The whole framework of MLR-NMF-RNN-LSTM yields the best results in terms of highest accuracy and lowest values of MAE, RMSE, and R^2.

Table 6. Ablation study of the proposed framework.

Model configuration	Accuracy (%)	MAE	RMSE	R^2
RNN-LSTM (without MLR & NMF)	91.42	0.0814	0.0963	0.9238
MLR + RNN-LSTM (without NMF)	94.28	0.0627	0.0715	0.9564
NMF + RNN-LSTM (without MLR)	95.36	0.0548	0.0641	0.9682
MLR + NMF + RNN-LSTM (Proposed)	97.99	0.0327	0.0427	0.9920

Figure 6 shows the general statistics of the correlation between experimental and estimated values of the proposed RNN-LSTM model based on NMF technique. The majority of the data points lie close to the reference line ($y = x$), showing a good level of correlation between the experimental and estimated values The high coefficient of determination (R^2) together with the low MAE and RMSE confirms that the proposed model accurately captures the relationship between pharmaceutical formulation parameters and drug release characteristics, demonstrating its robustness and prediction reliability.

The capability of a trained presentation of deep learning for the drug release profiles prediction was utilized. From these experimental results, trained, validated, and tested NMF-based RNN-LSTM could provide enhanced prediction performance of drug release kinetics.

Although the proposed NMF-based RNN-LSTM model achieved high prediction accuracy, it has certain limitations. The molecular descriptors and manufacturing process parameters were not considered in the present study. Future research will focus on incorporating more diverse pharmaceutical datasets, additional formulation characteristics, and advanced deep learning architectures to further

improve the model's robustness and generalization capability.

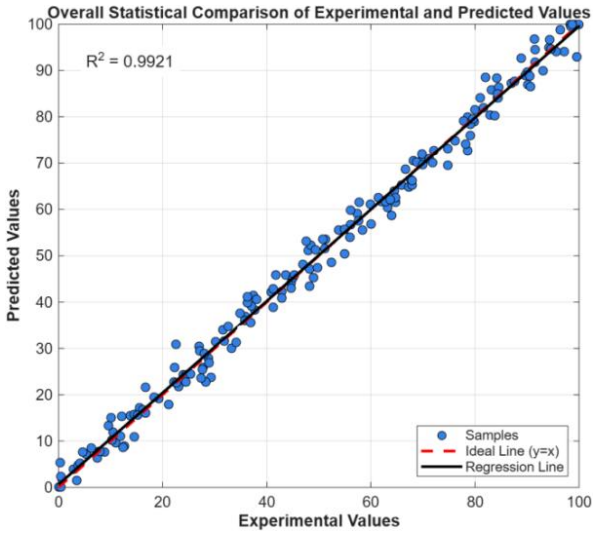

Figure 6. Overall statistical comparison between experimental and predicted values.

5. Conclusion

In this work, an NMF-based RNN-LSTM prediction model was proposed to analyze and predict drug release profiles. The dataset was taken from the Web of Science for the experimental study. In the first phase, data cleaning is accomplished with the help of the MRA method to attain more data quality. Drug release-based characteristics were extracted by applying the NMF scheme. RNN-LSTM has been trained with NMF-extracted features to predict drug release kinetics. Finally, drug release factors such as drug hardness, disintegration time, and dissolution rate were recognized through performance matrices MAE, RMSE, accuracy, and R^2. This study has estimated three drug release factors efficiently, such as hardness of drug, drug disintegration time, and drug dissolution rate, by the examination of pharmaceutical data including factors of drug formulation and physicochemical properties. The presented DL predictive tool has demonstrated that the NMF-based RNN-LSTM scheme could predict drug release kinetics effectively. These experimental results support drug research works to expansively observe the drug release profiles before the drug development process.

Author contributions: Conceptualization, MB, CR and KG; methodology, MB; validation, CR and KG; formal analysis, KG; investigation, CR; resources, MB; writing— MB; writing— KG; supervision, CR. All authors have read and agreed to the published version of the manuscript.

Funding: None.

Ethical approval: Not applicable.

Informed consent statement: Not applicable.

Conflict of interest: The authors declare that they have no conflict of interest.

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