Arabian Journal of Chemistry (2022) **15**, 104180

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Novel numerical simulation of drug solubility in supercritical CO_2 using machine learning technique: Lenalidomide case study

Rami M. Alzhrani [a,*], Atiah H. Almalki [b,c], Saleh l. Alaqel [d], Sameer Alshehri [a]

[a] *Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia*
[b] *Depaertment of Pharmaceutical Chemistry, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia*
[c] *Addiction and Neuroscience Research Unit, College of Pharmacy, Taif University, Al-Hawiah, Taif 21944, Saudi Arabia*
[d] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, Saudi Arabia*

Received 14 June 2022; accepted 7 August 2022
Available online 11 August 2022

KEYWORDS

Supercritical fluid;
Solubility Optimization;
Lenalidomide;
Numerical modeling

Abstract In pharmaceutical industry, finding promising ways to enhance the solubility of disparate types of drugs is an important challenge for the orally administered drug delivery system. Disparate techniques based on drug characteristics, nature of dosage form and properties of excipients have recently been under extensive evaluation all over the world to improve the solubility of poorly water-soluble drugs. Among them, supercritical fluid carbon dioxide (SC-CO_2) has received paramount attentions due to having considerable advantages like cost-effectiveness and low flammability. Lenalidomide belongs is an orally administered anti-cancer agent, which has recently received indication for the treatment of adult patients with different bone marrow-related malignancies such as multiple myeloma, mantle cell lymphoma and follicular lymphoma. Predicting the optimized value of Lenalidomide inside the SC-CO_2 in a wide range of pressure and temperature via developing mathematical models based on artificial intelligence (AI) is the main objective of this paper. In this study, three different machine learning based models are selected to predict and optimized the drug solubility. The available data includes 28 rows of data with two inputs including temperature and pressure and two outputs including density and solubility. Selected models are Kernel Ridge Regression (KRR), least angle regression (LAR), and Multilayer Perceptron (MLP). After optimizing models and comparing the results, the MLP was selected as the primary model of this research.

* Corresponding author.
E-mail address: r.zhrani@tu.edu.sa (R.M. Alzhrani).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.arabjc.2022.104180

The models illustrated R-squared scores of 0.999 and 0.994 for density and solubility. The maximum errors are also 2.92 and 6.44 × 10^{-2} for these outputs, which shows the accuracy and significant generality of the model.

1. Introduction

A determinative parameter in pharmaceutical industry, which significantly affects the performance and efficiency of a developed medicine is drug solubility (Kneller, 2010; Drews and Ryser, 1997; Padervand, 2017). This parameter possesses an incontrovertible role in specifying the desired concentration of a drug to obtain the necessary pharmacological response (Nguyen, 2022; Batchelor, 2022; Padervand et al., 2020).

With the aim of increasing drug solubility, various techniques including particle size reduction, application of surfactants, supercritical fluids (SCFs) and solid dispersion have been employed (Sareen et al., 2012; Girotra et al., 2013; Chaudhari and Dugar, 2017; Padervand et al., 2021). Among the approaches, the application of carbon dioxide SCF (SC-CO_2) has been more attractive after 1980 s due to its encouraging properties such as low cost, simplicity of use and low toxicity/flammability (Hannay and Hogarth, 1880; Dohrn, 2007; Padervand and Elahifard, 2017).

Lenalidomide (Revlimid®) is a well-known antineoplastic/angiogenesis inhibitor, which has received various indications by the U.S food and drug administration (FDA) and the European medicines agency (EMA) for the treatment of adult patients suffering from certain types of bone marrow-related malignancies such as multiple myeloma and myelodysplastic syndromes (MDS) (Padervand, 2021). Table 1 comprehensively renders the molecular structure and properties of Lenalidomide (Palumbo, 2012; Zeldis, 2011).

Machine learning (ML) is an artificial intelligence (AI) discipline that consists of a set of techniques that aid in the comprehension of patterns in data without making any assumptions about the data's structure. Building nonlinear correlations in data, as well as the interaction between predictors, is one of these methodologies' strengths (Senders, 2018; Cherkassky and Ma, 2003; Carbonell et al., 1983; Goodfellow et al., 2016). In this research, three approaches are selected as a novel approach to make models on the solubility dataset using Python (3.9) software. Selected models are Kernel Ridge Regression (KRR), Least angle regression (LAR), and Multilayer perceptron (MLP). Those models have been used as a novel method for the first time to optimize the solubility of Lenalidomide.

Least Angle Regression provides linear regression model coefficient routes with understandable geometrical interpretation. LAR's solution routes are piecewise linear and hence highly efficient to compute. This gives the algorithm with tremendous computational benefits over other variable selection approaches. LAR selects the predictor variable which is most associated with the response variable, and a regression coefficient update proceeds in this manner, starting with all coefficients equal to 0 (Lee and Jun 2018; Madigan and Ridgeway, 2004).

The Kernel Ridge Regression employs both ridge regressions and the kernel technique (KRR). Through regularization and kernel approaches, KRR provides the benefit of capturing nonlinear connections while avoiding regression over-fitting concerns (McDonald, 2009; Zhang et al., 2013). Also, a nonlinear mapping between input and output vectors is examined by the multilayer perceptron. It is made up of basic linked components known as neurons or nodes. Each neuron has a straightforward task to complete (Mielniczuk and Tyrcha, 1993; Noriega, 2005).

3.Materials and Method.

In this section, we will discuss the data used as well as the models that have been used in this research as the main structure of the analysis performed in more detail.

1.1. Data set

The data set analyzed in this study, which is taken from (Sajadian, 2022), has 28 rows of data whose inputs are temperature and pressure and whose outputs are solubility and density, as shown in Table 2. For more visibility, the pairwise relationship of the parameters is visualized in Fig. 1. Also, the Pearson Correlation (PC) Plot and Kendall Correlation Plot are shown in Fig. 2.

1.2. Models

Least angle regression (LAR) (Efron, 2004) is an effective variable selection approach. Expressly, it aims to pick the predictors (in our example, the basis polynomials) which have the largest influence on the estimator response $Y \equiv \mathscr{M}(\boldsymbol{X})$ from a potentially vast range of alternatives. LAR ultimately produces a sparse PC approximation, i.e., one with fewer terms than a traditional complete representation.

More specifically, LAR gives a collection of PC representations, where the first *meta*-model comprises a single estimator, the second contains two estimators, and so on. Following that, a criterion for picking the "best" *meta*-model is presented. A cross validation routine is used to estimate the correctness of each *meta*-model generated by LAR. Eventually, the *meta*-model with the highest estimate is preserved. Its sparsity is substantially smaller than the cardinality of the entire candidate basis. Finally, adaptive procedures that rely on repe-

Table 1 Molecular structure and physicochemical properties of Lenalidomide (File:Lenalidomide ball-and-stick.png., 2020; Semeraro, 2013; Wikipedia contributors., 2022).

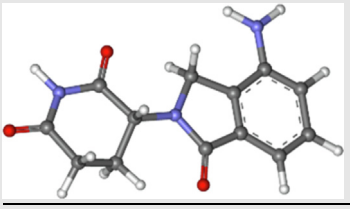
Molecular structure	Chemical formula	CAS number	Molecular weight	Route of administration
	$C_{13}H_{13}N_3O_3$	191732–72-6	259.265 g·mol^{-1}	Oral

Table 2 Solubility and Density data of at different temperatures (T) and pressures (P).

No.	T (K)	P (bar)	Density (kg m^{-3})	Solubility ($\times 10^4$) (mole fraction)
1	308	120	768.42	0.17
2	308	150	816.06	0.22
3	308	180	848.87	0.31
4	308	210	874.40	0.36
5	308	240	895.54	0.45
6	308	270	913.69	0.56
7	308	300	929.68	0.70
8	318	120	659.73	0.09
9	318	150	743.17	0.17
10	318	180	790.18	0.30
11	318	210	823.71	0.39
12	318	240	850.10	0.51
13	318	270	872.04	0.67
14	318	300	890.92	0.83
15	328	120	506.85	0.04
16	328	150	654.94	0.14
17	328	180	724.13	0.31
18	328	210	768.74	0.44
19	328	240	801.92	0.58
20	328	270	828.51	0.80
21	328	300	850.83	0.94
22	338	120	384.17	0.02
23	338	150	555.23	0.10
24	338	180	651.18	0.32
25	338	210	709.69	0.52
26	338	240	751.17	0.72
27	338	270	783.29	0.93
28	338	300	809.58	1.08

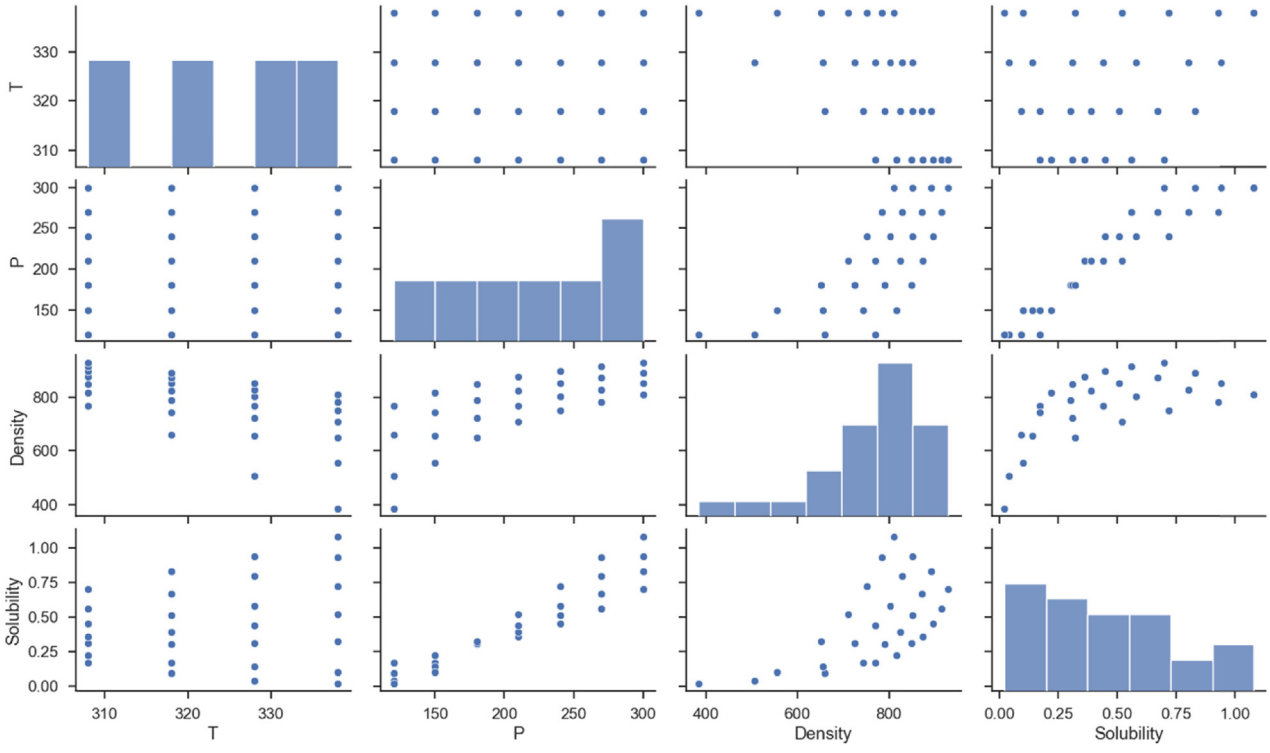


Fig. 1 Pairwise Distribution.

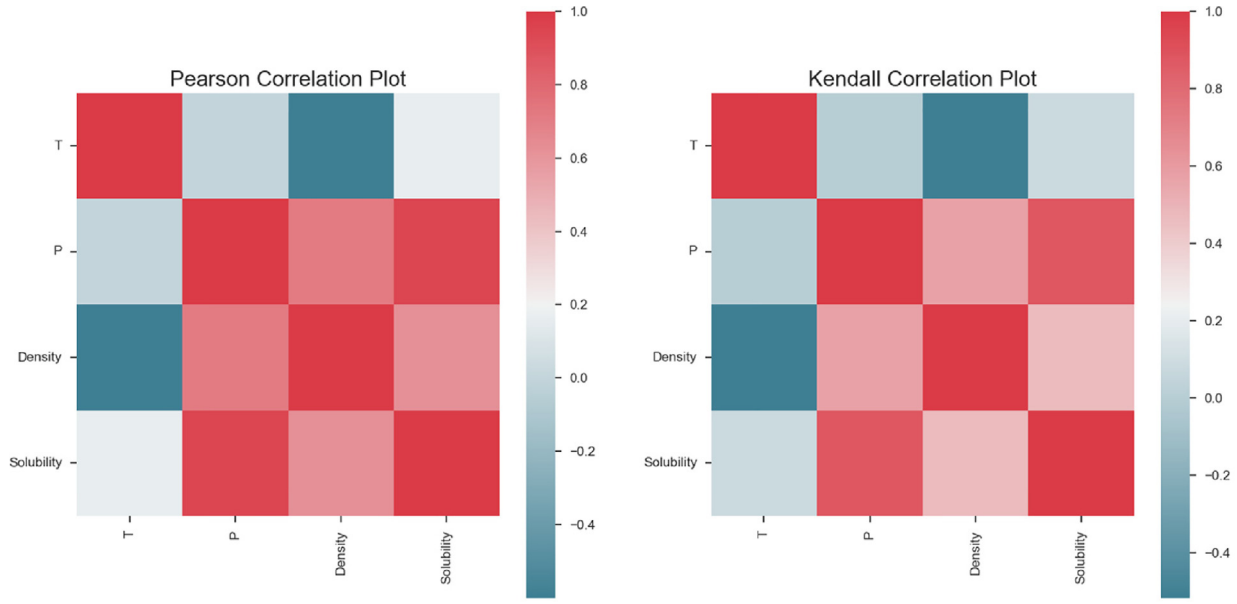


Fig. 2 Correlation Plots.

titions of the LAR procedure are described in full (Blatman and Sudret, 2011). The below algorithm summarizes the LAR regression steps:

1. Set the coefficients to $a_{\alpha_0}, \cdots, a_{\alpha_{P-1}} = 0$.
2. Initialize residual to the Y vector of training data.
3. Find the vector ψ_{α_j} that has the highest correlation with the present residual.
4. Change ψ_{α_j} from 0 to the least square coefficient of the current residual on ψ_{α_j} until another predictor ψ_{α_k} has the same correlation with the current residual as ψ_{α_j}.
5. Change a $\{a_{\alpha_j}, a_{\alpha_k}\}^T$ together in the direction given by their joint least square coefficient of the current residual on $\left\{\boldsymbol{\psi}_{\alpha_j}, \boldsymbol{\psi}_{\alpha_k}\right\}$ until some other predictor $\boldsymbol{\psi}_{\alpha_l}$ shows the same correlation with the current residual.

Go on this manner until $m \equiv \min\ (P,\ N-1)$ estimators are entered.

The active coefficients are "moved" toward their least square value in steps 3 and 4. It is equivalent to amending the form $\hat{a}^{(k+1)} = \hat{a}^{(k)} + \gamma^{(k)}\widetilde{w}^{(k)}$ (Efron, 2004; Khan et al., 2007).

The LAR descent direction and step are denoted by vector $\widetilde{w}^{(k)}$ and coefficient $\gamma^{(k)}$. As shown, both values may be obtained algebraically. It is important to mention that if $N \geqslant P$, then the ordinary least-square solution is provided by the final stage of LAR.

Kernel ridge regression (KRR), the other approach employed, is centered on ridge regression and ordinary least squares (OLS) regression. Suppose a data set $\{(x_i, y_i)\}_{i=1}^N$ is given and contains N data points pulled from an undetermined distribution $\mathbb{P}$ over $X \times \square$. The objective is to predict a function that optimizes the MSE of the data $[(f(x)-y)^2]$, where the expectation is taken jointly over (X, Y) pairs. The conditional mean $f^*(x) := \mathbb{E}[Y|X=x]$ is widely accepted as the best function (Byrne and Schniter, 2016). To predict the undetermined function f^*, An alternative solution is to use an M−estimator with least squares loss over the dataset and a weighted penalty based on the squared Hilbert norm (Vovk, 2013);

$$\widehat{f} := \underset{f \in H}{\operatorname{argmin}} \left\{ \frac{1}{N} \sum_{i=1}^{N} (f(x_i) - y_i)^2 + \lambda ||f||_H^2 \right\} \tag{1}$$

In the above equation, greater than 0λ is a regularization parameter and H indicates a reproducing kernel Hilbert space, the estimator is determined as the kernel ridge regression estimate, or KRR for short (Zhang et al., 2013). It is a natural non-parametric extension of the traditional ridge regression estimate (Hoerl and Kennard, 1970).

The multilayer perceptron analyzes a nonlinear mapping between input and output vectors. It comprises a group of simple interconnected units called neurons or nodes. There is a simple job that each neuron must do.

In contrast, neurons with many connections can solve complex and challenging problems that are not linear. Neurons are usually placed in layers. Multilayer Perceptron (MLP) is frequently used as an input layer, followed by numerous hidden layers, and finally an output layer. All these structures are called Multilayer Perceptron networks (Mucherino et al., 2009).

When paired with other training methods, the Levenberg–Marquardt algorithm produced the greatest accuracy when compared to gradient-based methods, and it was selected for network testing due to its quicker convergence. Sigmoid-log and tangent-sigmoid are the most often used model ANN activation functions, as is BP (Back Propagation). The input elements (x_i), weight (w_{ij}), bias (b_j), and $F(Y)$ are represented in the following equations. Function or output is the value (Deo and Şahin, 2015).

These three models have some important hyper-parameters that we optimize them using Grid Search method that tests different combinations to find the best combination. These hyper-parameters are listed in Table 3.

2. Results

To optimize models with their Hyper-parameters, different combinations examined, and the final models implemented. The final values are listed in Table 4.

Table 3 Hyper-Parameters.

Model	Hyper-Parameters
LAR	• AlphaFit intercept
KRR	• AlphaFit interceptSolverTolerance
MLP	• Hidden layer sizesActivationSolverTolerance

Table 4 Final Hyper-Parameters.

Model	Hyper-Parameters for Solubility	Hyper-Parameters for Density
LAR	• Alpha: 0.0009Fit intercept: False	• Alpha: 0.1478Fit intercept: True
KRR	• Alpha: 0.19653Fit intercept: TrueSolver: sagTolerance: 14.2303	• Alpha: 0.01993Fit intercept: TrueSolver: autoTolerance: 12.7768
MLP	• Hidden layer sizes: 32Activation: reluSolver: lbfgsTolerance: 0.00237	• Hidden layer sizes: 28Activation: logisticSolver: lbfgsTolerance: 0.0245

Table 5 R-squared scores for Final Model Results.

Models / Output	Density	Solubility
KRR	0.416	0.957
LAR	0.682	0.875
MLP	0.999	0.994

After tuning of models, the evaluation is done with multiple numeric and visual method. In Table 5 the R-square (Coefficient of Determination) scores of final models are displayed. This metric is used on a regression line to determine how close the predicted values are to the true (expected) values (Botchkarev, 2018).

$$R^2 - score = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \mu)^2} \tag{2}$$

Table 6 Error Rates for Final Model Results.

Metric	Mean Absolute Error (MAE)		Root Mean Square Error (RMSE)		Mean Absolute Percentage Error (MAPE)		Max Error	
output	Density	Solubility	Density	Solubility	Density	Solubility	Density	Solubility
KRR	4.37E + 01	5.92E-02	8.05E + 01	7.04E-02	9.54E-02	8.33E-01	1.97E + 02	1.16E-01
LAR	4.40E + 01	8.53E-02	7.58E + 01	1.00E-01	9.49E-02	9.41E-01	1.80E + 02	1.89E-01
MLP	1.30E + 00	1.80E-02	1.59E + 00	2.77E-02	2.23E-03	5.54E-01	2.92E + 00	6.44E-02

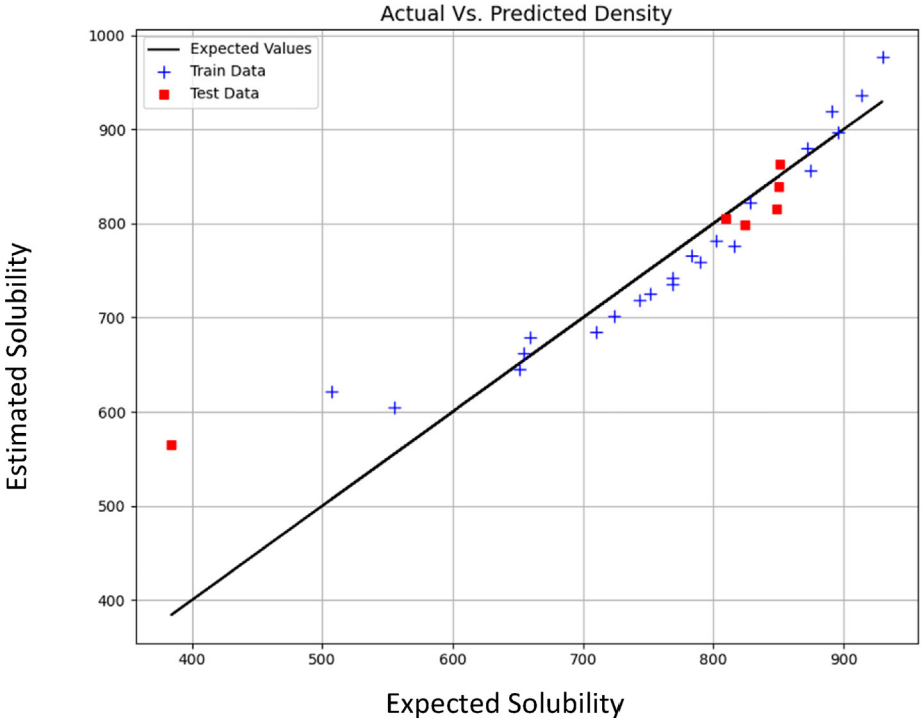


Fig. 3 Expected vs Estimated values of Density (kg m^{-3}) (KRR model).

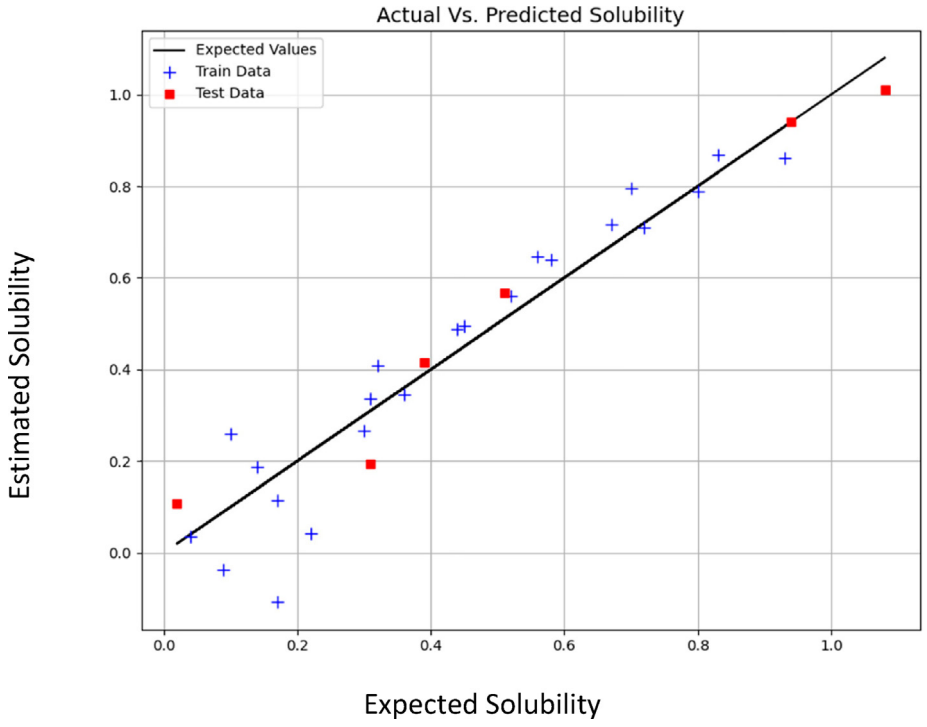


Fig. 4 Expected vs Estimated values of Solubility (mole fraction) (KRR model).

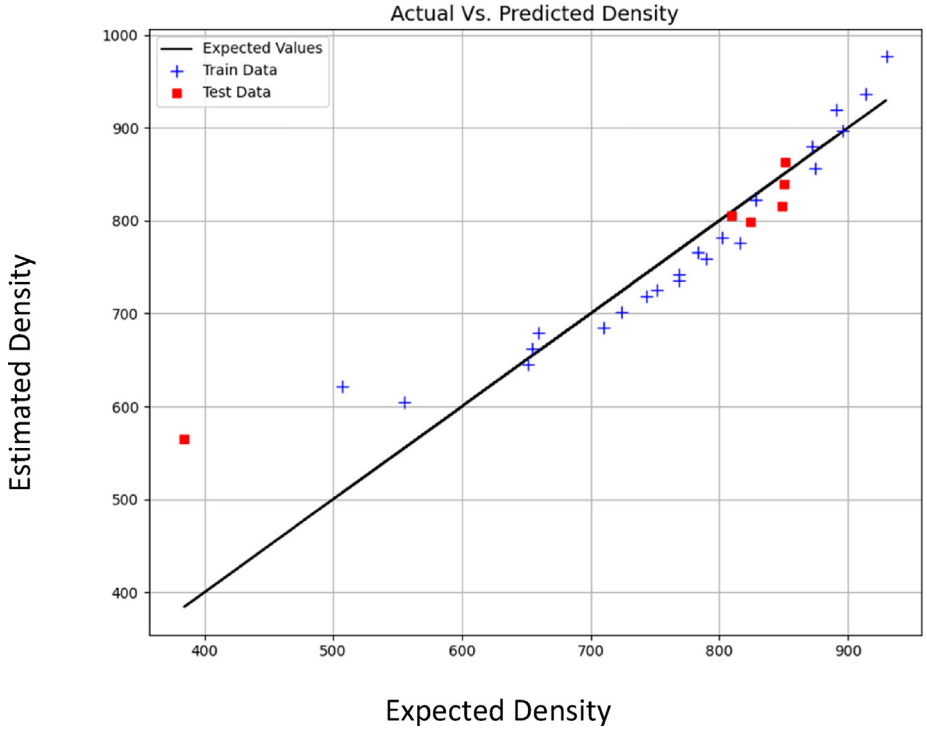


Fig. 5 Expected vs Estimated values of Density (kg m^{-3}) (LAR model).

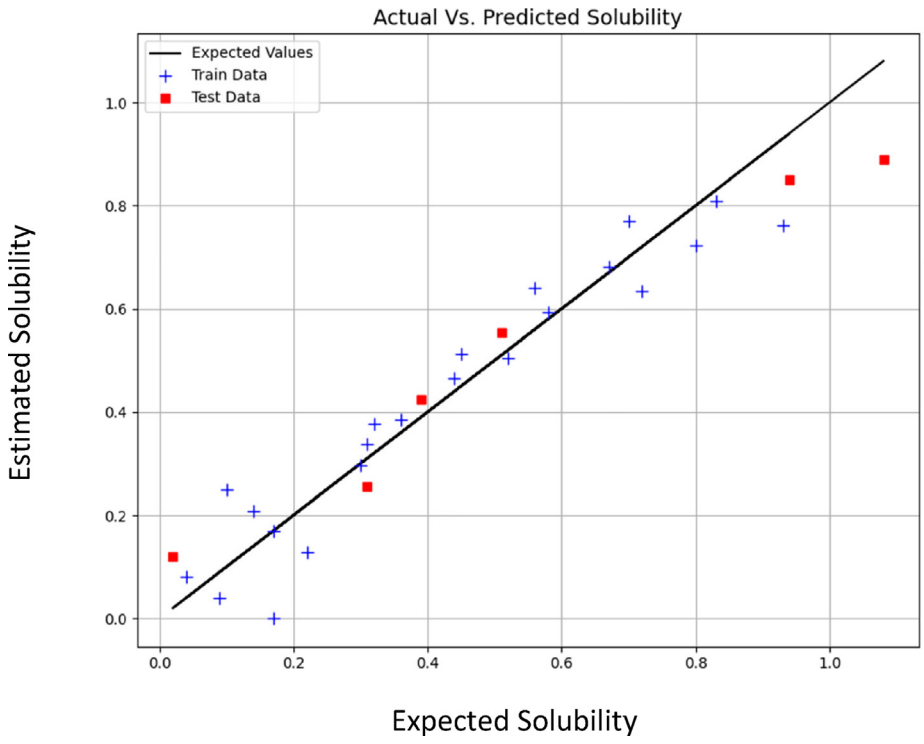


Fig. 6 Expected vs Estimated values of Solubility (mole fraction) (LAR model).

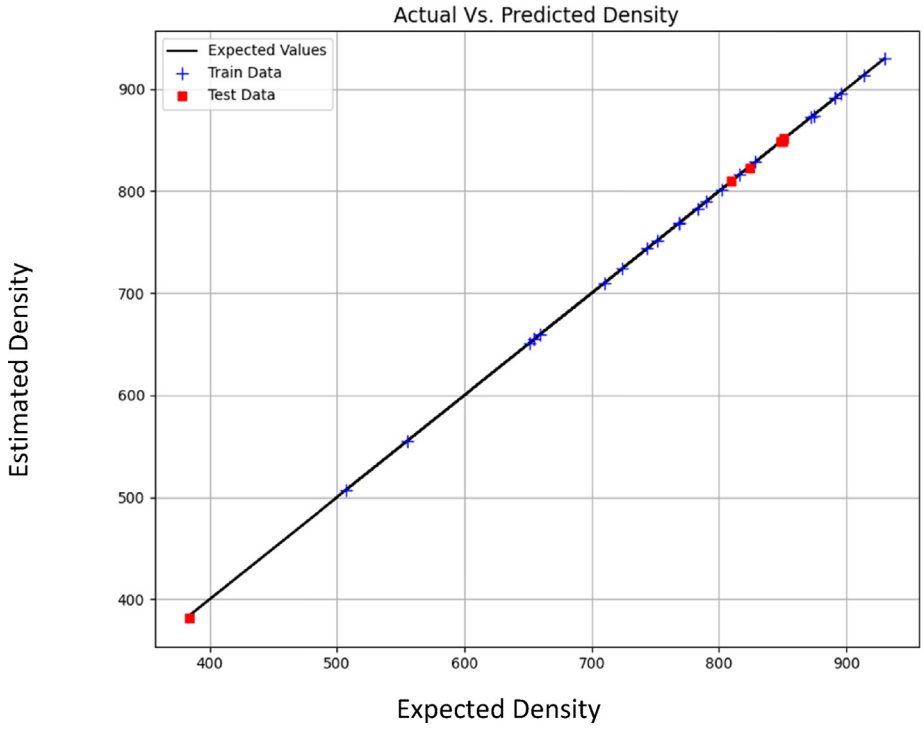


Fig. 7 Expected vs Estimated values of Density (kg m^{-3}) (MLP model).

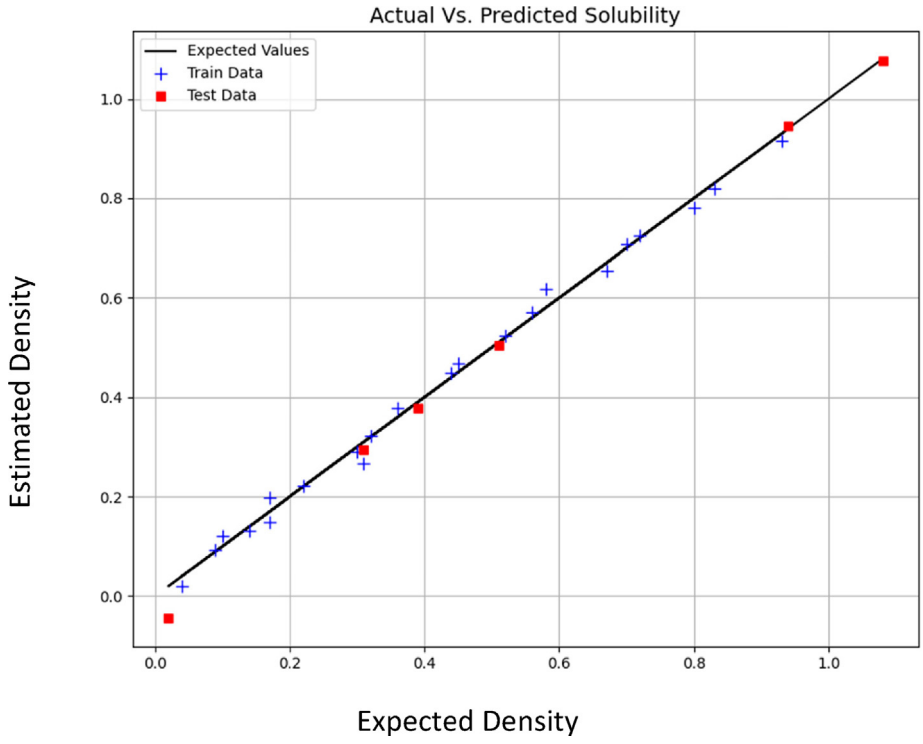


Fig. 8 Expected vs Estimated values of Solubility (mole fraction) (MLP model).

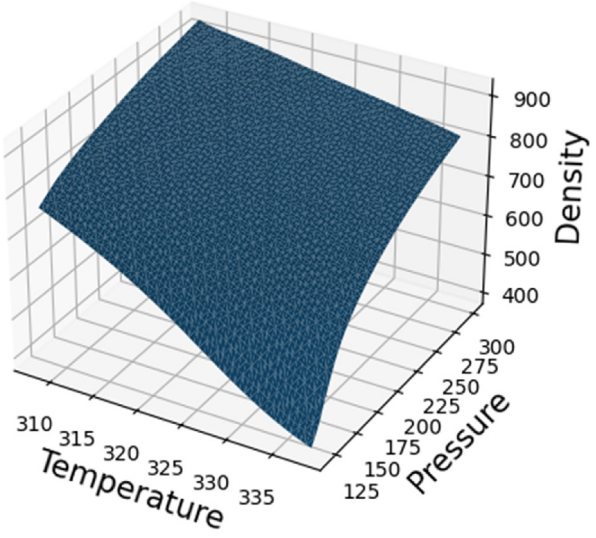


Fig. 9 Final prediction surface for density.

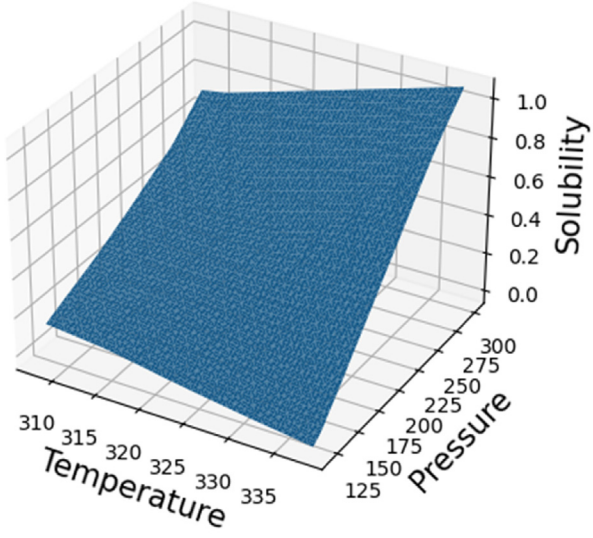


Fig. 10 Final prediction surface for solubility.

Where, μ indicates the mean of the expected data. For solubility prediction both KRR and MLP methods have scores more than 0.95 but for density prediction the only accurate model is MLP.

Error Rates of models are also displayed in Table 6 with metrics such as Mean Absolute Error (MAE), Mean Absolute Percentage Error (MAPE), and Maximum Error (De Myttenaere, 2016; Paula, 2020):

$$MAE = \frac{1}{n} \times \sum_{i=1}^{n} |\hat{y}_i - y_i| \tag{3}$$

$$MAPE = \frac{1}{n} \times \sum_{i=1}^{n} |\frac{\hat{y}_i - y_i}{y_i}| \tag{4}$$

Figs. 3 to 8 schematically compare the expected and predicted values. In these figures, the black line shows the expected values, red squares indicate the test data and sign plus denotes the train data. According to Table 6, the MLP model has the least errors in all cases for both outputs. Also, in Figs. 3–8, the visual comparison of expected and predicted val-

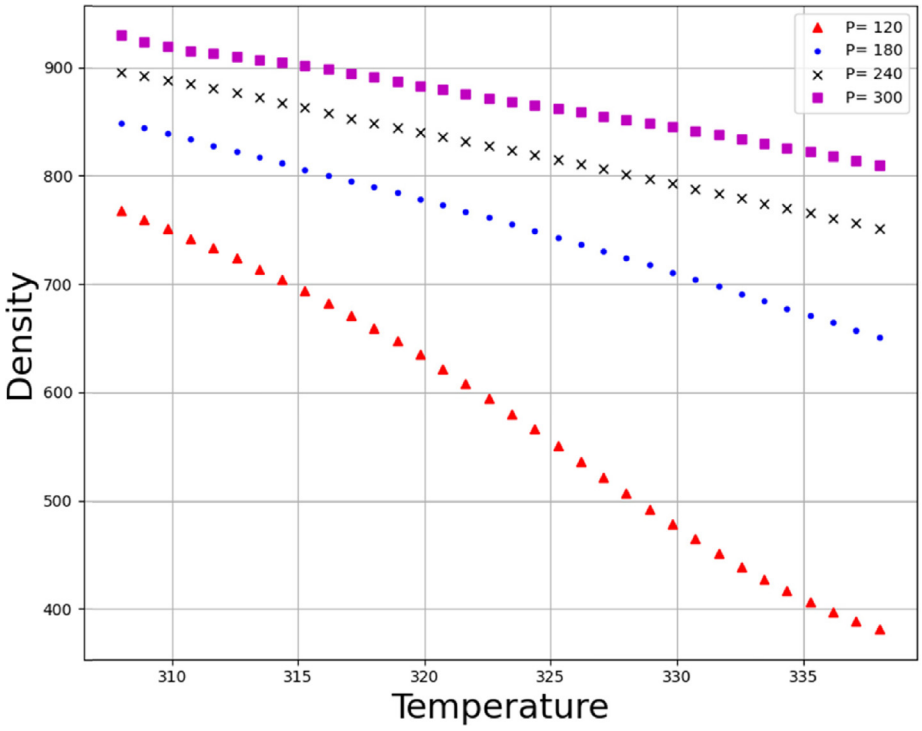


Fig. 11 Density Trends of Temperature (K) on different values of Pressure (bar).

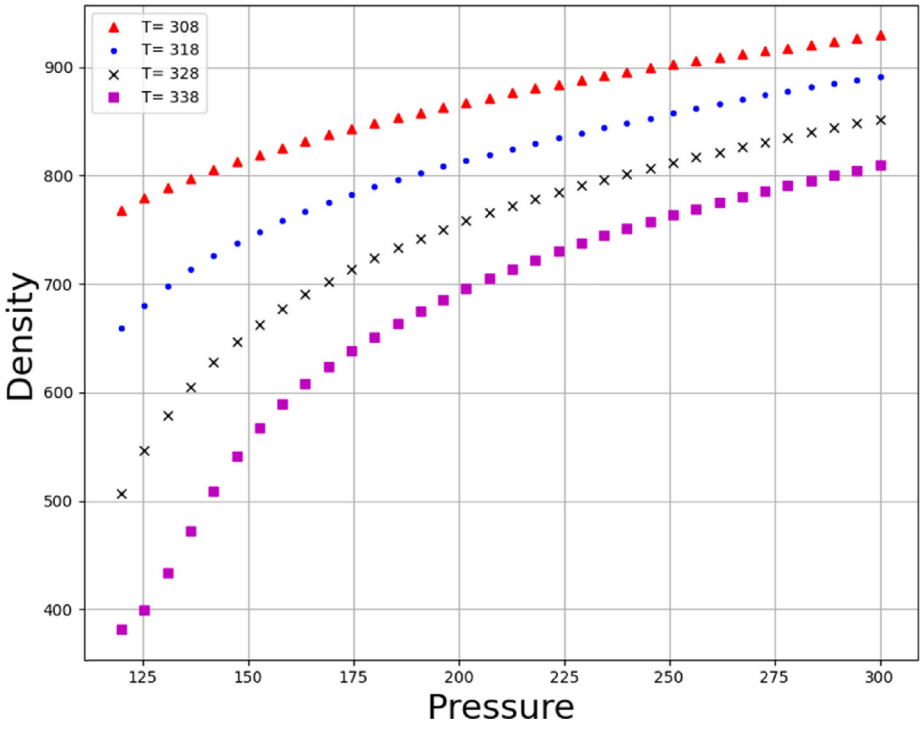


Fig. 12 Density Trends of Pressure (bar) on different values of Temperature (K).

ues is displayed. All these figures together confirm the fact that MLP is the most accurate and general model. Therefore, MLP was selected as the main model for both outputs in this study.

Figs. 9 and 10 demonstrate the simultaneous effects of temperature and pressure on the density and solubility of Lenalidomide based on MLP model. By looking at the figures, it can be understood that increment of pressure directly improves the Lenalidomide solubility in SC-CO_2 system. Increment of pressure possesses encouraging impact on the density of solvent, which frequently improves the

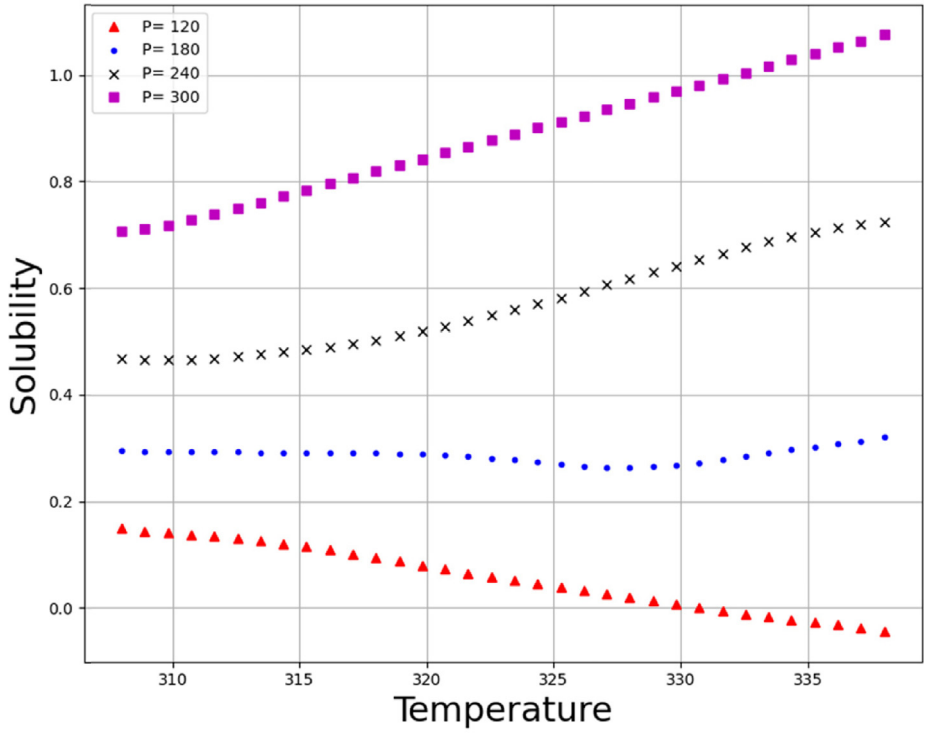


Fig. 13 Solubility Trends of Temperature (K) on different values of Pressure (bar).

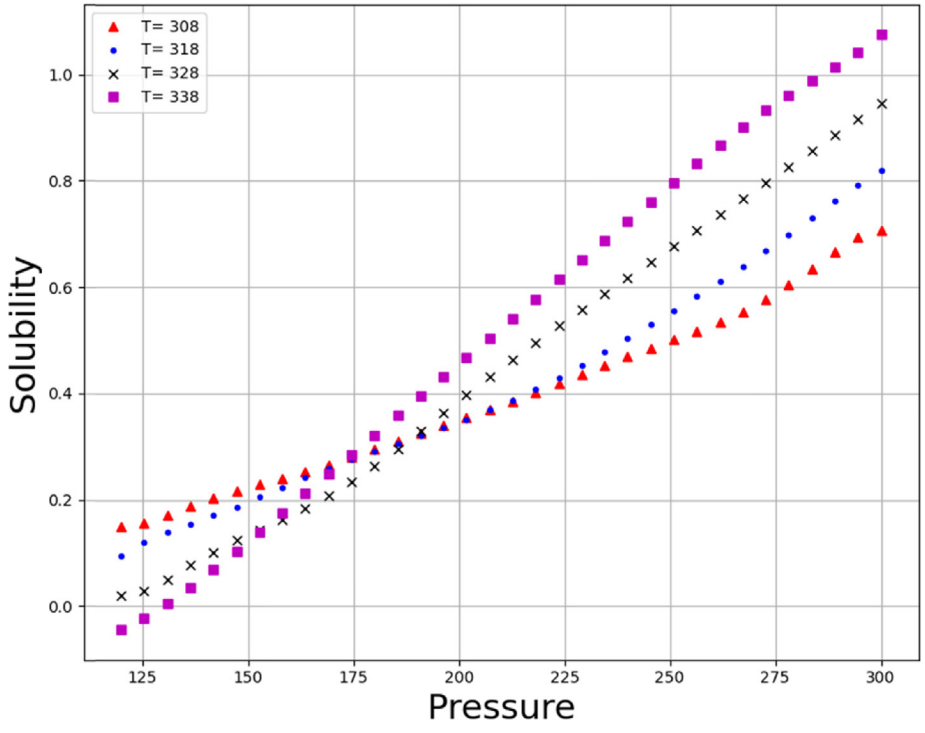


Fig. 14 Solubility Trends of Pressure (bar) on different values of Temperature (K).

solvating strength of the SC-CO_2 and thus, improves the solubility of drug. Despite the positive effect of pressure on the solubility of drugs, there is a paradoxical trend in the connection of temperature and solubility. As can be seen in Figs. 11, 12, 13 and 14, increase in pressure results in a significant enhancement in the compactness of solvent, which is attributed to greater density and superior solvating power of SC-CO_2 as solvent. With the aim of assessing the effect of temperature on Lenalidomide solubility, study on the role of two factors including sublimation pressure and

density above and below the cross-over pressure (COP) is of prime importance. By increasing the temperature at the pressures above the COP, the positive effect of sublimation pressure on Lenalidomide solubility overcomes the destructive influence of density reduction by increasing temperature. In doing so, at the pressures above the COP, increase in the temperature significantly improves the solubility of drugs in SC-CO_2 system. At the pressures less than the COP, the deteriorative effect of density decrement is greater than the encouraging impact of sublimation pressure. Thus, at these pressures, increment of the temperature dramatically declines the solubility Lenalidomide in SC-CO_2 solvent (Alshehri, 2022).

3. Conclusion

Application of SC-CO_2 as a robust, cost-effective, and versatile solvent has been of great attention in current decades. The prominent objective of this research was applying machine learning (ML) models to investigate and create a model for the density and solubility of Lenalidomide in SC-CO_2. The data that is currently available consists of 28 rows, including two inputs temperature and pressure. Both density and solubility are produced as the results. Kernel Ridge Regression (KRR), Least Angle Regression (LAR), and Multilayer Perceptron are some of the models that have been selected (MLP). The MLP was ultimately chosen as the primary model for this research after it was optimized and compared to several other models. The R-squared scores for our model are 0.999 for density and 0.994 for solubility. Both metrics are highly accurate. In addition, the maximum errors for these outputs are both 2.92 and 6.44 $\times$ 10^{-2}, which demonstrates both the precision and significant generality of the model. In terms of MAPE the model has error rate of 2.23 $\times$ 10^{-3}on density and 5.54 $\times$ 10^{-1} on solubility.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Rami M. Alzhrani would like to acknowledge Taif University Research Supporting Project Number (TURSP-2020/209), Taif University, Taif, Saudi Arabia.

References

Batchelor, H., 2022. *Solubility*. Biopharmaceutics: From Fundamentals to Industrial Practice, p. 39-50.

Alshehri, Sameer et al, 2022. Design of predictive model to optimize the solubility of Oxaprozin as nonsteroidal anti-inflammatory drug. Scientific Reports 12,. https://doi.org/10.1038/s41598-022-17350-5. In this issue 13106.

Blatman, G., Sudret, B., 2011. Adaptive sparse polynomial chaos expansion based on least angle regression. J. Comput. Phys. 230 (6), 2345–2367.

Botchkarev, A., 2018. *Evaluating performance of regression machine learning models using multiple error metrics in azure machine learning studio*. Available at SSRN 3177507.

Byrne, E., Schniter, P., 2016. Sparse multinomial logistic regression via approximate message passing. IEEE Trans. Signal Process. 64 (21), 5485–5498.

Carbonell, J.G., Michalski, R.S., Mitchell, T.M., 1983. An overview of machine learning. Machine learning, 3–23.

Chaudhari, S.P., Dugar, R.P., 2017. Application of surfactants in solid dispersion technology for improving solubility of poorly water soluble drugs. J. Drug Delivery Sci. Technol. 41, 68–77.

Cherkassky, V., Ma, Y., 2003. Comparison of model selection for regression. Neural Comput. 15 (7), 1691–1714.

De Myttenaere, A. et al, 2016. Mean absolute percentage error for regression models. Neurocomputing 192, 38–48.

Deo, R.C., Şahin, M., 2015. Application of the extreme learning machine algorithm for the prediction of monthly Effective Drought Index in eastern Australia. Atmos. Res. 153, 512–525.

Dohrn, R. et al, 2007. Melting point depression by using supercritical CO2 for a novel melt dispersion micronization process. J. Mol. Liq. 131, 53–59.

Drews, J., Ryser, S., 1997. Drug Development: The role of innovation in drug development. Nat. Biotechnol. 15 (13), 1318–1319.

Efron, B. et al, 2004. Least angle regression. The Annals of statistics 32 (2), 407–499.

File:Lenalidomide ball-and-stick.png. (2020, September 16). Wikimedia Commons, the free media repository. Retrieved 12:42, June 6, 2022 from https://commons.wikimedia.org/w/index.php?title=File:Lenalidomide_ball-and-stick.png&oldid=461504637.

Girotra, P., Singh, S.K., Nagpal, K., 2013. Supercritical fluid technology: a promising approach in pharmaceutical research. Pharm. Dev. Technol. 18 (1), 22–38.

Goodfellow, I., Bengio, Y., Courville, A., 2016. Machine learning basics. Deep learning 1 (7), 98–164.

Hannay, J., Hogarth, J., 1880. I. On the solubility of solids in gases. Proc. R. Soc. London 30 (200–205), 178–188.

Hoerl, A.E., Kennard, R.W., 1970. Ridge regression: Biased estimation for nonorthogonal problems. Technometrics 12 (1), 55–67.

Khan, J.A., Van Aelst, S., Zamar, R.H., 2007. Robust linear model selection based on least angle regression. J. Am. Stat. Assoc. 102 (480), 1289–1299.

Kneller, R., 2010. The importance of new companies for drug discovery: origins of a decade of new drugs. Nat. Rev. Drug Discovery 9 (11), 867–882.

Lee, S., Jun, C.-H., 2018. Fast incremental learning of logistic model tree using least angle regression. Expert Syst. Appl. 97, 137–145.

Madigan, D., Ridgeway, G., 2004. *Discussion of" Least angle regression" by Efron et al*. arXiv preprint math/0406469.

McDonald, G.C., 2009. Ridge regression. Wiley Interdiscip. Rev. Comput. Stat. 1 (1), 93–100.

Mielniczuk, J., Tyrcha, J., 1993. Consistency of multilayer perceptron regression estimators. Neural Networks 6 (7), 1019–1022.

Mucherino, A., Papajorgji, P.J., Pardalos, P.M., 2009. K-nearest neighbor classification. In: Data Mining in Agriculture. Springer, pp. 83–106.

Nguyen, H.C. et al, 2022. Computational prediction of drug solubility in supercritical carbon dioxide: Thermodynamic and artificial intelligence modeling. J. Mol. Liq. 354, 118888.

Noriega, L., 2005. Multilayer perceptron tutorial. Staffordshire University, School of Computing.

Padervand, M. et al, 2017. Reverse phase HPLC determination of sunitinib malate using UV detector, its isomerisation study, method development and validation. J. Anal. Chem. 72 (5), 567–574.

Padervand, M. et al, 2021. Preferential Solvation of Pomalidomide, an Immunomodulatory Drug, in Some Biocompatible Binary Mixed Solvents at 298.15 K. Russ. J. Phys. Chem. A 95 (12), 2432–2443.

Padervand, M., Elahifard, M.R., 2017. Development of a spectrophotometric method for the measurement of kinetic solubility: economical approach to be used in pharmaceutical companies. Pharm. Chem. J. 51 (6), 511–515.

Padervand, M., Naseri, S., Boroujeni, H.C., 2020. Preferential solvation of pomalidomide, an anticancer compound, in some binary mixed solvents at 298.15 K. Chin. J. Chem. Eng. 28 (10), 2626–2633.

Padervand, M., Naseri, S., Hajiahmadi, S., 2021. Preferential solvation and solvation shell composition of sunitinib malate, an anti-tumor compound, in some binary mixed solvents at 298.15 K. Chem. Pap. 75 (3), 939–950.

Palumbo, A. et al, 2012. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N. Engl. J. Med. 366 (19), 1759–1769.

Paula, M. et al, 2020. Predicting Long-Term Wind Speed in Wind Farms of Northeast Brazil: A Comparative Analysis Through Machine Learning Models. IEEE Lat. Am. Trans. 18 (11), 2011–2018.

Sajadian, S.A. et al, 2022. Experimental analysis and thermodynamic modelling of lenalidomide solubility in supercritical carbon dioxide. Arabian J. Chem. 15, (6) 103821.

Sareen, S., Mathew, G., Joseph, L., 2012. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int. J. Pharm. Invest. 2 (1), 12.

Semeraro, M. et al, 2013. Trial watch: lenalidomide-based immunochemotherapy. Oncoimmunology 2 (11), e26494.

Senders, J.T. et al, 2018. Machine learning and neurosurgical outcome prediction: a systematic review. World Neurosurg. 109, 476–486.

Vovk, V., 2013. Kernel ridge regression. In: Empirical Inference. Springer, pp. 105–116.

Wikipedia contributors. 2022, May 27. Lenalidomide. In Wikipedia, The Free Encyclopedia. Retrieved 12:48, June 6, 2022, from https://en.wikipedia.org/w/index.php?title=Lenalidomide&oldid=1090079965.

Zeldis, J.B. et al, 2011. A review of the history, properties, and use of the immunomodulatory compound lenalidomide. Ann. N. Y. Acad. Sci. 1222 (1), 76–82.

Zhang, Y., Duchi, J., Wainwright, M., 2013. *Divide and conquer kernel ridge regression*. In: *Conference on learning theory*. PMLR.