PROSPECTS
IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 23(3), 97-109
https://prospects.wum.edu.pl/

Original Article

LIQUISOLID TECHNIQUE FOR SOLUBILITY ENHANCEMENT OF A POORLY SOLUBLE THROMBIN INHIBITOR: OPTIMIZATION USING DESIGN OF EXPERIMENTS AND ARTIFICIAL NEURAL NETWORKS

Rama Devi Korni*[1], Thanmaisree Bora[1], Akhil Majji[1], Jagadeesh Panda[1], Sre Meghna Killana[2]

[1] *Raghu College of Pharmacy, Dakamarri, Visakhapatnam - 531162 Andhra Pradesh, India.*

[2] *GITAM School of Technology, GITAM University, Visakhapatnam - 531162 Andhra Pradesh, India.*
* Correspondence, e-mail: ramakalyank@gmail.com

Received: 18.12.2025 / Revised: 06.02.2025 / Accepted: 01.03.2025 / Published: 03.10.2025

ABSTRACT

The current work uses liquisolid (LS) technology to increase the absorption efficiency and dissolution rate of the weakly water-soluble drug dabigatran etexilate (DE) by formulating it using the design of experiments (DoE) and comparing it with the artificial neural network (ANN). D-optimal design in Stat-Ease software was used to formulate and optimize DE liquisolid capsules. The drug-to-nonvolatile solvent ratio (X1 – 25 to 50), carrier-to-coating ratio (X2 – 10 to 30), type of nonvolatile solvent (X3 – PEG 400 or Kolliphor EL) and type of carrier (X4 – Neusilin or Fujicalin) were taken as independent variables and percentage drug release (Y1) and angle of repose (Y2) were taken as dependent variables. The results were compared to artificial neural networks (ANN) utilizing JMP software to improve the prediction of the chosen output variables. The optimized formulation was developed and evaluated. The R^2 value of the D-optimal design for percentage drug release was 0.914, whereas for ANN, it was 0.943. The mean square error (MSE) value of the quadratic model obtained in the D-optimal design was 90.76, and in ANN, it was only 2.392. The R^2 value for the quadratic model in the D-optimal design for the angle of repose was 0.723, whereas for ANN, it was 0.751. The MSE for the D-optimal design was 28.11, whereas for ANN, it was 11.04. Based on the analysis of results, PEG400 was selected as the nonvolatile solvent and Neusilin as a carrier for optimized formulation. The percentage drug release and angle of repose of optimized DE liquisolid capsules were found to be 86.23 ± 1.37 and 36.08 ± 0.63, respectively. XRD studies indicated a reduction in the crystallinity of the drug in liquisolid formulations. The findings suggested that dabigatran etexilate's solubility rate could be increased by using liquisolid capsules. ANN gave better predictability than the design of experiments.

KEYWORDS: Liquisolid, design of experiments, D-optimal design, artificial neural networks, JMP.

1. Introduction

A strong synthetic non-peptide competitive thrombin inhibitor, dabigatran is a member of the Biopharmaceutical Classification System (BCS) class II. Due to its poor absorption following oral administration, it is provided as a prodrug. The anticoagulant dabigatran etexilate (DE) is inert. Following oral consumption, non-specific DE esterases in the liver and plasma activate this prodrug. The first direct thrombin inhibitor approved by the FDA is dabigatran etexilate, a fast-acting, low-molecular-weight, reversible medication used to treat atrial fibrillation-related stroke and systemic embolism and to prevent venous thromboembolism (VTE) following knee and hip surgery [1]. The solubility of DE is strongly influenced by pH, increasing at acidic pH levels. DE's poor solubility and P-gp efflux result in low bioavailability (7.2%) after oral dosing. To improve the oral bioavailability of dabigatran etexilate, several works have been reported employing various formulation techniques, including the solid self-micro emulsifying drug delivery system [2], the drug-phospholipids complex nano-emulsion [3], and the Soluplus®-TPGS binary mixed micelles system [4].

Drug solubility plays a vital role in assessing its bioavailability. Nearly 70% of newly developed drugs and 40% of commercial novel pharmaceuticals in oral formulations have exhibited limited water solubility. Oral drug delivery is favored due to its advantages in patient compliance, convenience, and cost-effectiveness. For optimal absorption, orally administered drugs must be adequately dissolved in gastric fluids. Drugs that demonstrate low solubility in these fluids are less readily absorbed, leading to diminished bioavailability. The enhancement of drug

dissolution performance and the development of formulations that ensure suitable bioavailability and therapeutic efficacy represent significant challenges currently confronting the pharmaceutical industry. Various methodologies, including micronization, nanonization, complexation with cyclodextrins, solid dispersion, self-emulsifying systems, and liquisolid systems, are under investigation to address these issues and improve dissolution performance and bioavailability [5,6].

A contemporary approach referred to as "powdered solution technology", commonly known as "liquisolid technology", has been employed to develop fast-acting solid dosage forms of drugs that are insoluble in water. The liquisolid process entails the combination of a liquid with a carrier and a coating agent to produce a free-flowing powder. Liquisolid systems consist of dry, non-adherent powder mixtures formed by integrating liquid drugs, suspensions, or solutions with carriers and coating materials in nonvolatile solvents [7]. Liquid medication is defined as a mixture of an insoluble substance and a solvent. A liquisolid formulation, which incorporates a solvent, is transformed into a dry, non-adhesive, and compressible powder by adding a diluent and a lubricant [8]. The process entails transforming a liquid or solid medication into a solubilized state. Ingesting a liquid that has been mixed with a drug facilitates its dissolution, while the incorporation of a carrier substance promotes absorption into the drug layer [9].

The medication that is solubilized in the nonsolvent is integrated into a carrier substance, which may include materials such as cellulose, Neusilin, or Fujicalin. This process facilitates both absorption and adsorption; initially, the liquid is absorbed within the particles, subsequently being retained by their internal framework. Following this initial phase, the adsorption of the liquid takes place on both the internal and external surfaces of the porous carrier particles once saturation is achieved. The essential flow properties of the liquisolid system are imparted by the coating material, which possesses high adsorptive capabilities and a substantial specific surface area. The liquisolid technique offers several advantages, including enhanced bioavailability, reduced production costs, regulated drug release, and consistent dissolution rates. A typical liquisolid formulation comprises the following key components: a non-volatile solvent, the drug candidate, carrier materials, coating materials, and a disintegrant [10].

Non-volatile solvents are characterized by their elevated boiling points. These solvents are inert organic systems that ideally possess water solubility and exhibit low viscosity. The development of liquisolid systems incorporates a range of nonvolatile solvents, including propylene glycol, polysorbate 80, glycerin, and Kolliphor EL. Medications encompass digoxin, digitoxin, dabigatran etexilate, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, as well as various liquid formulations such as chlorpheniramine, water-insoluble vitamins, and fish oil, among others, which serve as examples of potential drug candidates. Liquid medications consist of lipophilic pharmaceuticals in liquid form, drug suspensions, and solutions containing solid, water-insoluble drugs dissolved in suitable nonvolatile solvent systems. Carrier materials typically consist of large, preferably porous particles that enhance compression and possess sufficient absorption capacity to facilitate liquid uptake. Examples of such materials include various grades of cellulose, starch, lactose, sorbitol, Avicel PH 102 and 200, Eudragit RL and RS, as well as amorphous cellulose. Coating materials possess the ability to adsorb surplus liquid, consisting of exceptionally fine particles ranging from 10 nm to 5,000 nm in diameter. These highly adsorptive coating agents, which include various grades of silica such as Cab-O-Sil M5, Aerosil 200, and Syloid 244FP, enhance flow properties and assist in enveloping the wet carrier particles, thereby creating the illusion of a dry powder. Commonly utilized disintegrants include sodium starch glycolate (such as Explotab13 and Pumogel) and starch, which are among the most frequently employed in formulations [11].

The advantage of an organic solvent-free preparation procedure of liquisolid technique and other advantages are the reasons for the choice of liquisolid capsules of DE to increase the drug solubility. Liqusolid technique has attempted to increase the solubility of DE mesylate by Prasanthi et al. DE mesylate liquisolid compacts were made with a non-volatile solvent mixture of span 80 and castor oil, coating material, Aerosil 200 in various ratios (R = 5, 10, 15, 20, 25), and carrier materials such as maize starch, MCC, Avicel pH 101 and 102, and Prosolv SMCC 50 with loading factors of 0.72, 0.75, 0.77, 0.87, and 1.75, respectively [12]. In the past work, optimization of the formulation was done based on the trial-and-error method which is time-consuming and there is no assurance of obtaining the optimized formulation. There is no work reported on the optimization of liquisolid capsules of dabigatran etexilate. The current work aimed to optimize the DE liquisolid formulation using two systematic statistical approaches, experimental design and Artificial Neural Networks (ANN). The current study optimized DE Liquisolid capsules utilizing D-optimal design. The formulations' angle of repose and percentage of drug release were measured and assessed. The optimized formulation was prepared and assessed.

2. Materials and Methods

2.1. Materials

Dabigatran etexilate was purchased from Yarrow Chem Products (Mumbai, Maharashtra 400086). Polyethylene glycol (PEG 400) was purchased from Merck Life Science Private Limited India. Kolliphor® EL [Polyoxyl 35 Castor Oil (USP-NF)] was a generous gift from BASF (Mumbai, India). Neusilin® US2 (magnesium aluminometasilicate) was a generous gift from Sunkem Industries. Fujicalin® (spherically granulated dicalcium phosphate anhydrous) was purchased from Himedia laboratories. All other chemicals and solvents were of analytical grade.

2.2. Solubility studies

The equilibrium solubility of dabigatran etexilate was assessed in several non-volatile solvents. Saturated solutions were prepared by adding an excess quantity of the drug (30 mg) to a fixed volume (5 ml) of each nonvolatile solvent. The resulting mixture was subjected to agitation at a temperature of 25 ± 1°C for 72 hours. Once equilibrium is reached, the mixture is subjected to centrifugation for 30 minutes using a centrifuge (REMI R4C). The supernatant was subjected to analysis for ultraviolet (UV) absorbance at 326 nm following dilution with 0.01 N HCl, and the quantity of the drug was subsequently determined.

A suitable solvent that demonstrated effective solubility for the drug was identified through solubility studies [13]. Preliminary solubility studies were initially performed to identify appropriate excipients with the highest potential for solubilizing the drug, thereby facilitating optimal drug loading [14,15]. The selection of the appropriate excipient was made from various non-volatile solvents, including glycerol, PEG 400, polysorbate 60, and Kolliphor EL. The solubility studies were also carried out in distilled water for comparison purposes.

2.3. Optimization of liquisolid capsules using D-optimal design

For the optimization of liquisolid formulation design, a trial version of Stat-Ease software (23.1.1 64-bit Stat-Ease, Inc., Minneapolis, MN) was utilized. Computer algorithms can generate a variety of design types, including the D-optimal design. These computer-aided designs are especially beneficial in scenarios where conventional designs may not be feasible. In D-optimal design matrices, effect estimates are correlated, which distinguishes them from traditional classical designs such as factorial and fractional factorial designs, which are typically orthogonal. The D-optimal design was utilized to formulate the trials in liquisolid formulation settings. This design was specifically applied to characterize the liquisolid formulations of dabigatran. The independent parameters selected were X1, X2, X3, and X4, representing the drug-to-nonvolatile solvent ratio, the carrier-to-coating ratio, the type of nonvolatile solvent, and the type of carrier, respectively. X1 and X2 are numerical factors and X3 and X4 are categorical factors. The concentrations of each component were established within predetermined ranges. The concentration of the drug to the non-volatile solvent is specified to be between 25% and 50%, while the ratio of carrier to coating is indicated to range from 10% to 30%. The dependent variables selected for this study include the percentage of drug release (Y1) and the angle of repose (Y2). A total of twenty-three experimental runs were conducted, including four duplicate runs performed at the center point, which were generated and assessed. The objective of this approach was to derive a model-independent estimate of the process standard deviation, thereby enhancing precision and quantifying experimental error. Following each response, a nonlinear equation was employed to align the data with a quadratic polynomial model. A model was deemed significant at the 5% significance level if its significance probability value, or p-value, fell below 0.05. Additionally, for every response that yielded an elevated F value, the corresponding fitted model was also recognized.

$$Y = \beta_0 + \beta_1X1 + \beta_2X2 + \beta_3X3 + \beta_4X4 + \beta_5X1X2 + \beta_6X3X4 + \beta_7X1X4 + \beta_8X1^2 + \beta_9X2^2 + \beta_{10}X3^2 + \beta_{11}X4^2 + E$$

where Y is the response of the dependent variables; β_0-β_9 are the regression coefficients; and X_1, X_2, X_3 and X_4 are independent variables [16,17]. The compositions of runs given by D-optimal design of DE liquisolid capsules are given in Table 1.

Table 1. Formulation of dabigatran etexilate liquisolid capsules

Formulations	Drug-to-nonvolatile solvent ratio (X1)	Carrier-to-coating ratio (X2)	Type of nonvolatile solvent (X3)	Type of carrier (X4)	Percentage drug release (Y1)	Angle of repose (Y2)
F1	50	22	Kolliphor EL	Neusilin	64.93	37.9
F2	39.5	18	PEG 400	Neusilin	91.98	37.3
F3	35.1349	10.1	PEG 400	Fujicalin	78.37	36.9
F4	48	11.8	Kolliphor EL	Neusilin	65.7	39.007
F5	50	22	PEG 400	Fujicalin	78.06	37.3
F6	25	18	PEG 400	Neusilin	83.98	34.44
F7	50	22	PEG 400	Fujicalin	76.06	37.9
F8	50	10	PEG 400	Neusilin	82.39	33.822
F9	27.25	28.5	PEG 400	Neusilin	82.47	34.2
F10	37.25	25.5	PEG 400	Fujicalin	75.4	33.822
F11	35.1349	10.1	PEG 400	Fujicalin	80.33	38.3
F12	50	22	Kolliphor EL	Neusilin	64.93	37.9
F13	25	30	Kolliphor EL	Neusilin	70.52	30.11
F14	50	10	Kolliphor EL	Fujicalin	75.27	36.129
F15	35	21.9	Kolliphor EL	Fujicalin	77.46	34.94
F16	25	30	PEG 400	Fujicalin	79.8	36.9
F17	35	21.9	Kolliphor EL	Fujicalin	77.46	34.99
F18	25	10	Kolliphor EL	Fujicalin	68.2	32.35
F19	47.5	20	Kolliphor EL	Fujicalin	66.24	37.3
F20	40	29.7653	PEG 400	Neusilin	85.27	33.9
F21	35	10.222	Kolliphor EL	Neusilin	71.63	36.9
F22	35	10.222	Kolliphor EL	Neusilin	71.63	37.3
F23	50	30	Kolliphor EL	Fujicalin	66.51	35.1

2.4. Artificial neural network

An artificial neural network (ANN) is a type of algorithm that determines associations by fitting discrete calculations made by artificial "neurons" into a bigger model. In an ANN, every neuron uses a different activation function to model data [18]. By adjusting the quantity and kind of activation functions, ANN can be made more efficient. Previous efforts to bioprocess ANN have demonstrated effectiveness, but they usually need coding expertise to execute and mostly rely on intricate machine-learning techniques. The artificial neural network was utilized to analyze the impact of input factors on output variables. Based on the artificial neural network, the effects of the input variables on output variables were also analyzed and the formula of DE liquisolid was optimized using JMP 15 software [19]. The pharmaceutical companies in the world can investigate process and lab data, comprehend the sources of process variation, gain additional insight from root-cause investigations, and optimize processes and experimental design — all without having to learn how to code, by using JMP data analysis software [20].

2.5. Application of mathematical model for designing DE liquisolid capsules

The "flowable liquid retention potential" (Φ-value) of a powdered material denotes its ability to retain a specific volume of liquid while maintaining desirable flow properties. This value represents the maximum amount of liquid that can be retained per unit weight of the powdered material, resulting in a liquid/powder mixture that exhibits satisfactory flow characteristics [11]. The liquid load factor can be calculated using the equation, $\varphi \mathrm{Lf} = \varphi \mathrm{CA} + \varphi \mathrm{CO}\frac{1}{R}$. The variables φCA and φCO represent the flowability of the liquid retention potential of the carrier and coating materials, respectively [21,22]. R denotes the excipient ratio. The liquid load factor is also given by the ratio of the weight of the liquid drug and the weight of the carrier material. Using the obtained liquid load factor value, the weight of the carrier material can be calculated. The carrier:coating ratio (R) is given by the ratio of the weight of the carrier material to the weight of the coating material. Using the obtained weight of carrier material, the weight of coating material can be obtained. Research published in various academic journals indicates that R-values between 10 and 30 yield optimal flow characteristics and satisfactory compactibility.

The φ values for Neusilin US2 and Aerosil 200 in PEG 400 are Lf = 1.45 + 2.5 (1/R) [23]. The φ values for Fujicalin and Aerosil 200 in PEG 400 are Lf = 0.05 + 1.68 (1/R) [22]. The φ values for Neusilin and Aerosil 200 in Kolliphor EL are Lf = 0.845 + 0.80 (1/R) [22]. The φ values for Fujicalin and Aerosil 200 in Kolliphor EL are Lf = 0.435 + 0.8 (1/R) [24].

2.6. Preparation of DE liquisolid capsules

The necessary quantity of the drug and non-volatile solvent was introduced into a glass beaker and mixed gradually until the drug was entirely dissolved. The non-volatile solvent acts as a conduit, promoting the efficient diffusion of drug molecules from the surface of dissolution into the surrounding medium. In contrast, formulations that consist solely of the active pharmaceutical ingredient lack this bridging mechanism entirely [25]. The "Noyes-Whitney" equation, $\frac{\mathrm{dC}}{\mathrm{dt}} = \frac{DS}{Vh}(C_s - C)$, suggests that a non-volatile liquid enveloping the particle within the liquisolid system may have facilitated the dissolution of additional drug in the stagnant diffusion layer. Here $\frac{\mathrm{dC}}{\mathrm{dt}}$ is the change in drug concentration over time, D is the diffusion coefficient, S is the effective surface area of the particles in contact with the dissolution medium, V is the volume of the dissolution medium, h is the thickness of the diffusion layer, C_s is saturation solubility and C is the concentration of drug in dissolution medium at time t.

This phenomenon results in a significant concentration gradient between the diffusion layer and the bulk medium, thereby enhancing drug dissolution [26]. The liquid medication obtained by mixing dabigatran etexilate in nonvolatile solvents (PEG 400 and Kolliphor EL) was combined with a specified quantity of either Neusilin or Fujicalin, which serve as carriers because their elevated porosity and specific surface area facilitate the absorption of the liquid into the pores of the particles, leading to a substantial liquid load. Aerosil 200 serves as coating material in the formulation of liquisolid preparations of dabigatran etexilate. Enhanced flowability is attributed to the sponge-like absorption of the liquid by the porous excipients, which increases the weight of the particles and enhances their flow characteristics [27].

In the initial phase, the powder excipient was mixed with the liquid medicament at an estimated rate of one rotation per second for approximately one minute to ensure uniform distribution of the liquid medication within the powder. During the subsequent phase, the powder mixture was spread evenly as a homogeneous layer on the surfaces of a mortar and allowed to rest for about five minutes, facilitating the absorption of the medication solution into the powder's internal matrix. In the final phase, the powder was removed from the mortar's surface using an aluminum spatula and combined with the disintegrating agent for an additional 30 seconds, following the procedure outlined in the first phase. The prepared granules were passed through a mesh. To these granules add starch. The completed liquisolid formulation was then encapsulated in size 00 capsules [28].

2.7. Studies of precompression parameters

The flowability of liquisolid admixtures is essential in the formulation of solid dosage forms at an industrial level. Therefore, before the compression process, it is important to evaluate the flowability of these liquisolid powder mixtures. Various parameters, such as Hausner's ratio, angle of repose, and Carr's index, can be employed to measure flowability [29]. Using the fixed height funnel approach, the powder blend's angle of repose was ascertained. To determine the angle of repose θ, the following formula was used: $\theta = \tan^{-1} h/r$; where h and r are the powder cone's height and radius. Carr's compressibility index was utilized to ascertain the powder blend's compressibility index. The following is the Carr's index formula:

$$\text{Carr's index } (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100.$$

Hausner's ratio was derived from the equation [30]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}.$$

2.8. Drug release study in-vitro

DE capsules containing 75 mg of the drug were used to carry out the dissolution studies. A USP type II paddle apparatus (LAB INDIA TDT 060) was utilized to conduct an in vitro drug release study of the dabigatran etexilate capsules at a temperature of 37°C ± 0.5°C, employing 900 mL of 0.01 N HCl as the dissolution medium and a rotation speed of 50 rpm. At regular intervals, 5 mL samples were withdrawn and replenished with fresh dissolution medium to maintain the sink conditions. The absorbance of these samples was measured at 326 nm using a UV spectrophotometer (LAB INDIA UV 3200). The cumulative percentage of drug release was calculated using an equation derived from a calibration curve [31].

2.9. Fourier transform infrared spectroscopy (FTIR) analysis

Pure drug DE and its liquisolid capsules' FTIR spectra were acquired. After carefully mixing 5 mg of sample with 100 mg of potassium bromide IR powder, the mixture was compressed under vacuum for three minutes at a pressure of around 12,000 psi. The resulting disk was placed in an appropriate holder within a Bruker (α2) infrared spectrophotometer, and throughout the course of a 12-minutes scan, the infrared spectrum was recorded between 4000 and 400 cm^{-1}. To check for any spectral alterations, the resulting spectra were compared [32].

2.10. X-ray diffraction (XRD) analysis

An X-ray powder diffraction (XRD) analyzer Bruker (D8 advance) was used to examine XRD patterns. The samples were examined across the 2θ range of 5-50 after being subjected to a 1.540 Å Cu radiation wavelength. XRD patterns were identified for a drug, and a drug-containing liquisolid system [32].

3. Results

3.1. Solubility studies

Selecting a nonvolatile solvent in which the drug is either molecularly dispersed or has a substantially smaller particle size than the pure crystalline form is the aim of the solubility studies. Preliminary solubility tests are carried out to determine the maximal potential for solubilizing the drug in order to determine which excipients are best for optimal drug loading. An appropriate excipient is selected from a variety of non-volatile solvents, including Kolliphor EL, PEG 400, polysorbate 60, and glycerol. The solubility of dabigatran etexilate in various solvents is Kolliphor EL (36.591 ± 1.52 mg/mL) > PEG 400 (26.905 ± 1.23 mg/mL) > Glycerol (3.302 ± 0.36 mg/mL) > Polysorbate 60 (1.022 ± 0.23 mg/mL). This is compared with its water (distilled water) solubility (0.1103 ± 0.012 mg/ml). The drug demonstrated limited solubility in glycerol and polysorbate 60. Based on the findings from the solubility tests, PEG 400 and Kolliphor EL were selected as the non-volatile solvents for further investigation due to their significant solubilization capabilities of DE. The greater the solubility of the drug in a nonvolatile solvent, the less nonvolatile solvent is needed to dissolve DE, and further, the less nonvolatile solvent will improve the blend's flow characteristics. The selection of these vehicles is also based on the safety and compatibility of the excipients with gelatin capsules [33]. The solubility studies of dabigatran etexilate in various nonvolatile solvents are given in Fig. 1.

3.2. Statistical analysis of results

The experiment was structured around four independent variables, designated as X1, X2, X3, and X4. The Design Expert software trial proposed a total of 23 formulations. Each formulation was prepared with a consistent quantity of the drug, ensuring that each contained 75 mg. The percentage of drug release after 60 minutes, along with the angle of repose,was measured for all 23 formulations to facilitate the analysis of the Design of Experiments [34]. As shown in Table 1, the percentage of drug release (Y1) varied from 64.93 to 91.98 and the angle of repose (Y2) varied from 30.11 to 39.007 for the 23 experimental runs. The Fraction of Design space is given in Fig. 2. It can be inferred from the graph that 68% of the design space had a prediction value of less than 0.68.

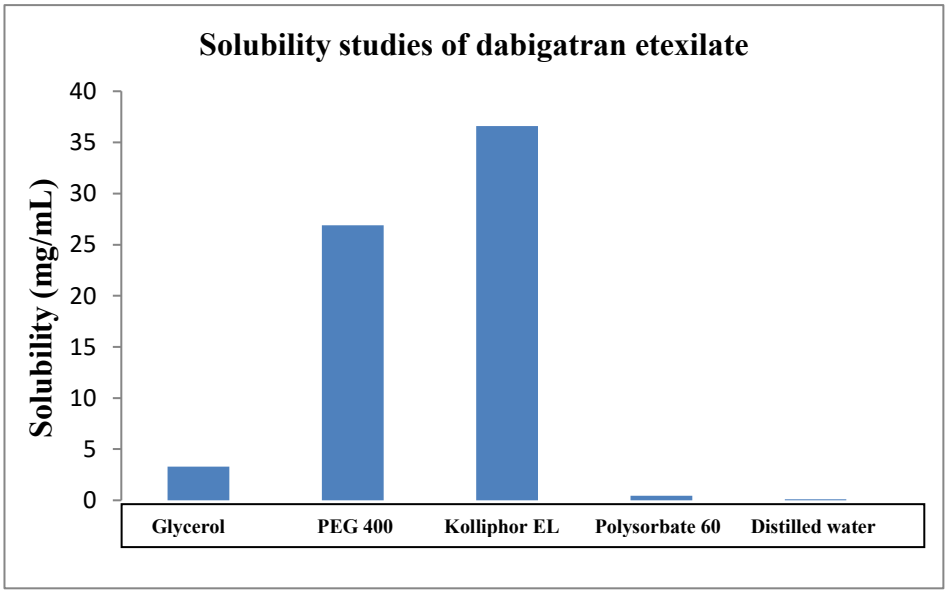

Fig. 1. Solubility studies of dabigatran etexilate in various nonvolatile solvents and distilled water

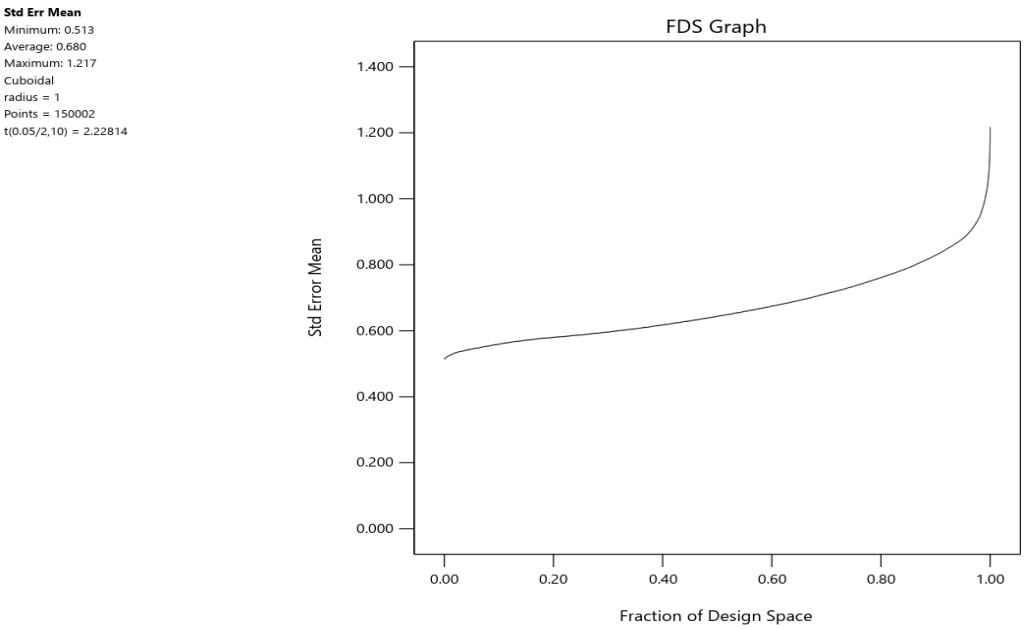

Fig 2. Fraction of design space

3.2.1. Percentage drug release

The model F-value of 8.85 (Table 2) indicates that the model is statistically significant. The probability of obtaining an F-value of this magnitude purely by chance is merely 0.08%. P-values below 0.0500 suggest that the model terms are statistically significant. Conversely, p-values exceeding 0.1000 imply that the model terms lack significance. The lack of fit F-value of 27.81 indicates that the lack of fit is statistically significant. There exists only a 0.12% probability that an F-value of this magnitude could arise purely from random variation. A significant lack of fit is undesirable, as it suggests that the model does not adequately represent the data. Furthermore, a negative predicted R^2 (Table 3) suggests that the overall mean may serve as a more effective predictor of the response variable than the current model. In certain instances, employing a higher-order model may yield improved predictions. Adequate precision assesses the signal-to-noise ratio, with a ratio exceeding 4 being preferable. The observed ratio of 9.549 signifies a satisfactory signal. Consequently, this model is suitable for exploring the design space. The selected model for percentage drug release was quadratic and its R^2 value was 0.9140, adjusted R^2 value of 0.8107, F-value of 8.85, and p-value of 0.0008 as given in Tables 2 & 3. The effect of independent variables on percentage drug release is given by the following polynomial equation: $Y1 = 79.25 - 1.37X1 - 0.3408X2 - 5.42X3 - 0.9538X4 - 2.86X1X2 - 0.5953X1X3 + 0.7875X1X4 - 0.2414X2X3 - 0.2247X2X4 + 2.93X3X4 - 4.34X1^2 - 1.22X2^2$. The coefficients of all the four independent variables X1, X2, X3, and X4 are negative which indicates a negative effect of the independent variables on percentage drug release. X1 and X2 indicate drug:nonvolatile solvent ratio and carrier:coating ratio. The coefficients of interaction terms X1X4 and X3X4 are positive which indicates an increase in percentage drug release with the combined effect of drug:nonvolatile solvent ratio, type of carrier, and type of nonvolatile solvent, type of carrier respectively. Contour plots and 3D surface plots, which are shown in Fig. 3, further clarified the effect of independent factors on the percentage drug release. Lower levels of X1 and X2 were found to be effective in increasing the drug release of DE from liquisolid capsules. PEG 400 containing formulations had shown higher drug release.

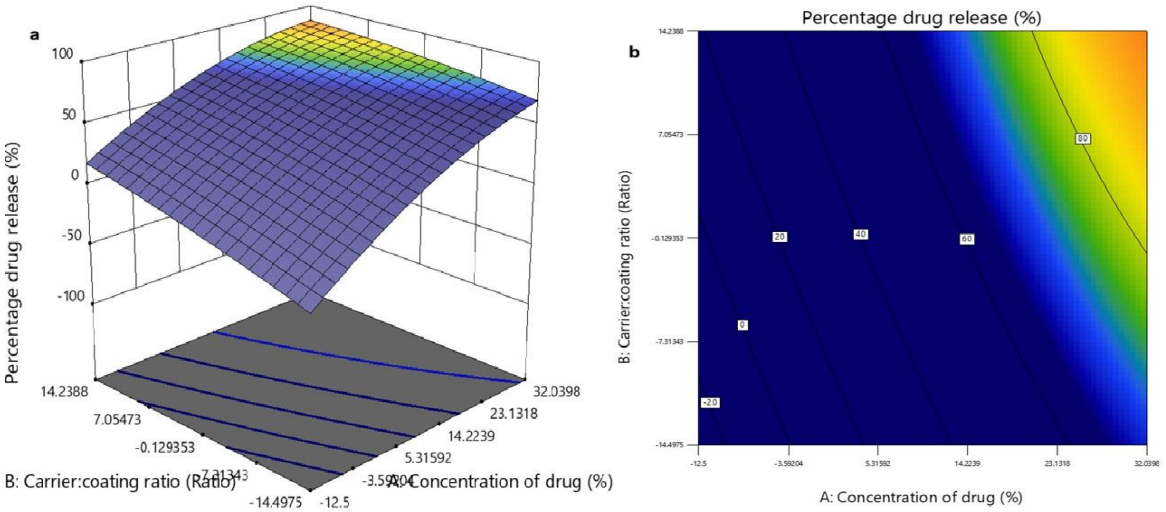

Fig. 3. a) 3D surface and b) Contour plots of percentage drug release

3.2.2 Angle of repose

The model F-value of 3.14 (Table 2) indicates that the model is statistically significant. The probability of obtaining an F-value of this magnitude purely by chance is merely 3.22%. P-values below 0.0500 suggest that the model terms are statistically significant. Conversely, values exceeding 0.1000 imply that the model terms lack significance. In cases where numerous model terms are insignificant (excluding those necessary to maintain hierarchy), reducing the model may enhance its overall performance. The lack of fit F-value of 15.91 indicates that the lack of fit is statistically significant. The probability of observing such a large lack of fit F-value purely by chance is merely 0.38%. A significant lack of fit is undesirable, as it suggests that the model does not adequately represent the data. A negative predicted R^2 suggests that the overall mean could serve as a more effective predictor of your response variable than the existing model. Additionally, in certain instances, a model of higher order may yield improved predictions. Adequate precision assesses the signal-to-noise ratio, with a ratio exceeding 4 being preferable. A ratio of 7.360 signifies a satisfactory signal. This model is applicable for exploring the design space. The selected model for percentage drug release was quadratic and its R^2 value was 0.7234, adjusted R^2 value of 0.4929, F-value of 3.14, and p-value of 0.0322 as given in Tables 2 & 3. The effect of independent variables on angle of repose is explained by the following polynomial equation: $Y2 = 36.49 + 1.12X1 - 1.03X2 - 0.3931X3 + 0.1853X4 + 0.2479X1X2 + 1.26X1X3 - 0.0679X1X4 - 0.3876X2X3 + 0.2828X2X4 - 0.8109X3X4 - 0.7134X1^2 - 1.14X2^2$. The coefficient of X1 (drug : nonvolatile solvent ratio) is positive, implying an increase in repose angle with an increase in drug : nonvolatile solvent ratio. The coefficient of carrier:coating ratio (X2) is negative which indicates a decrease in the angle of repose with an increase in carrier : coating ratio, thereby improving flow property [35]. Contour plots and 3D surface plots, which are shown in Fig. 4, further clarified the relationship between independent and dependent factors on the angle of repose. Due to its superior capacity for liquid adsorption, formulations that include Neusilin have demonstrated enhanced flow characteristics. This facilitates the preparation of liquisolid systems for high-dose, poorly soluble medications that necessitate substantial volumes of liquid vehicles. The angle of repose was significantly influenced by the choice of carrier or coating material.

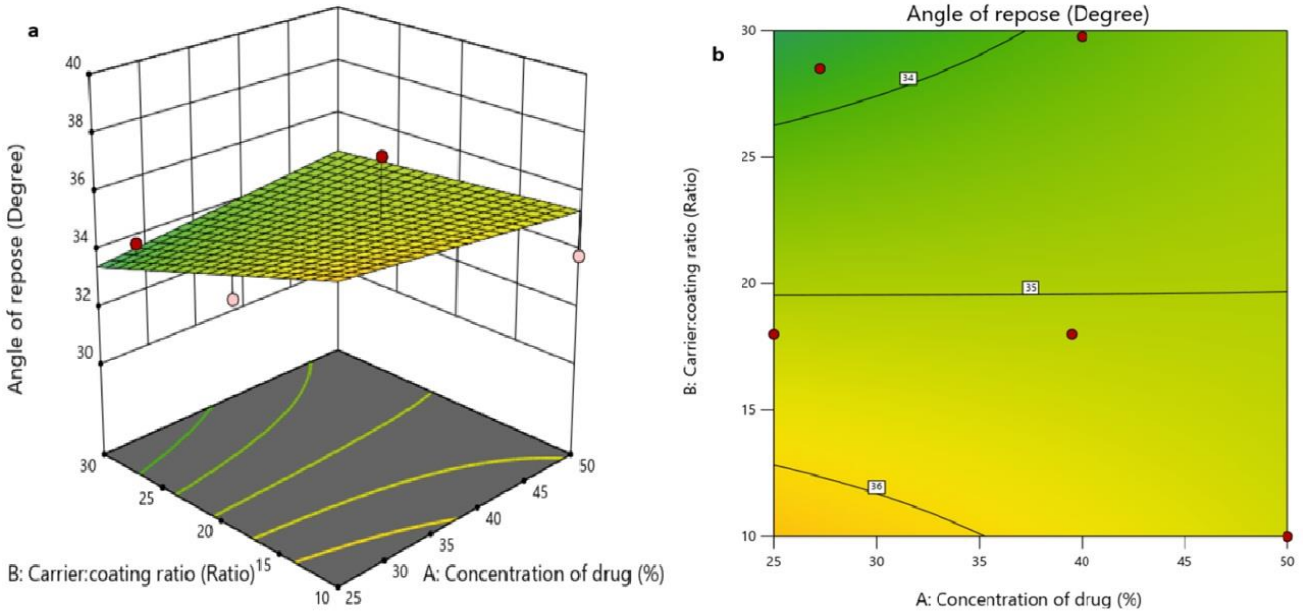

Fig. 4. a) 3D surface and b) Contour plots of the angle of repose

Table 2. Statistical analysis of results

Dependent variables		Sum of squares	DF	Mean square	F- value	P-value
Percentage drug release (Y1)	Model	1199.75	12	99.98	8.85	0.0008
	Residual	112.94	10	11.29		
	Lack of fit	109.02	5	21.80	27.81	0.0012
	Pure error	3.92	5	0.7842		
	Cumulative total	1312.69	22			
Angle of repose (Y2)	Model	75.49	10	7.55	3.14	0.0322
	Residual	28.86	12	2.41		
	Lack of fit	27.62	7	3.95	15.91	0.0038
	Pure error	1.24	5	0.2480		
	Cumulative total	104.35	22			

Table 3. Statistical analysis of responses

Quadratic model	R^2	Adjusted R^2	Predicted R^2	Adequate precision	SD	%CV
Percentage drug release (Y1)	0.9140	0.8107	-0.2857	9.5494	3.36	4.44
Angle of repose (Y2)	0.7234	0.4929	-1.2698	7.3595	1.55	4.32

3.2.3. Formulation optimization using the desirability function

Based on the desirability value, the DE liquisolid formulation with a high percentage drug release and angle of repose was optimized. The formulation with the maximum attractiveness value of 1 was made, and the angle of repose and percentage of drug release were calculated. The drug : nonvolatile solvent ratio of 25 and the carrier : coating ratio of 20 are the numerical components of the optimal formulation composition. The design obtained a lower ratio of drug:nonvolatile solvent and medium level of carrier: coating ratio to obtain optimizing DE liquisolid capsules with a higher percentage drug release and lower angle of repose. The percentage drug release was found to be higher in formulations containing PEG 400 as a nonvolatile solvent as compared to Kolliphor El. The angle of repose values was lower in formulations containing Neusilin as a carrier indicating a better flow property compared to Fujicalin. Thereby, PEG 400 (nonvolatile solvent) and Neusilin (carrier) were selected as categorical factors for obtaining optimized formulation. The Stat-Ease software projected that the angle of repose would be 34.9329 and the percentage of medication release would be 85.771. For the optimized formulation, the calculated percentage drug release and angle of repose were 86.23 ± 1.37 and 36.08 ± 0.63, respectively.

3.3. ANN

Based on responses, Y_1 and Y_2, the model was analyzed in JMP 15 software.

3.3.1. Structure of ANN

Fitting of the ANN feed forward back propagation framework's structure to the D-optimal design data was done. There were nineteen training sets, two validation sets, and two testing sets in the data set. Levenberg-Marquardt topology was used to train the network, resulting in a high R-value by minimising the error sum of squares for the training data set. To minimise the network performance function, the network's weights and biases were iteratively changed during training. The constructed network's default performance function is the mean square error (MSE). Gradient descent with momentum was used as the learning function because the momentum enables the network to disregard minute details in the error surface. The validation dataset's MSE was used to determine how many training cycles were needed [35]. The structure of ANN is given in Fig. 5.

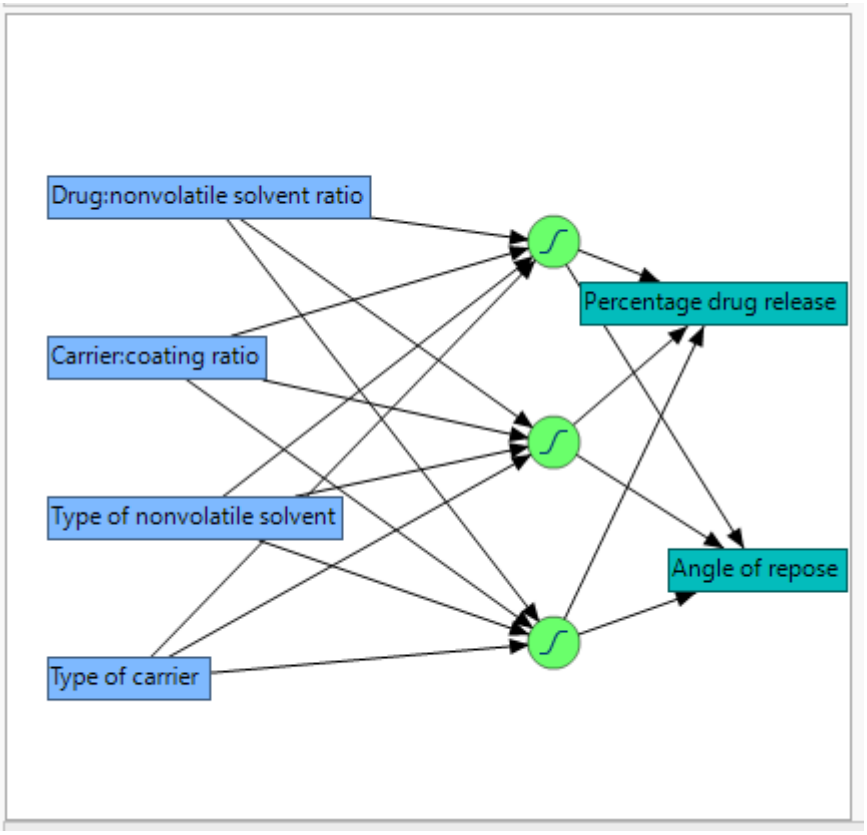

Fig. 5. Artificial neural network structure of JMP software

3.3.2. Regression

The neural network dataset's regression revealed a high R^2 value. As a percentage of drug release the regression coefficient's overall combined value was determined to be 0.943, which was more than the quadratic model of D-optimal design's regression coefficient value of 0.914. This demonstrated that the ANN model was trained to produce superior outcomes to the experiment's D-optimal design. As a proportion of the angle of repose the regression coefficient's overall combined value was determined to be 0.751, which was higher than the quadratic model of D-optimal design's regression coefficient value of 0.723. This demonstrated that the ANN model was trained to produce superior outcomes to the experiment's D-optimal design. After analysis, the actual by the predicted plot for training and validation datasets of percentage drug release and angle of repose were shown in Fig. 6 & 7, respectively.

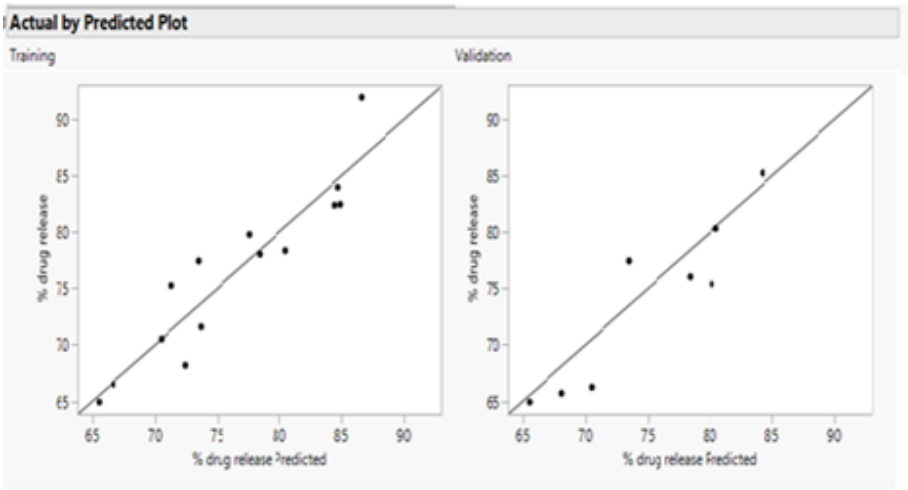

Fig. 6. Actual vs predicted percentage drug releasegiven by JMP software

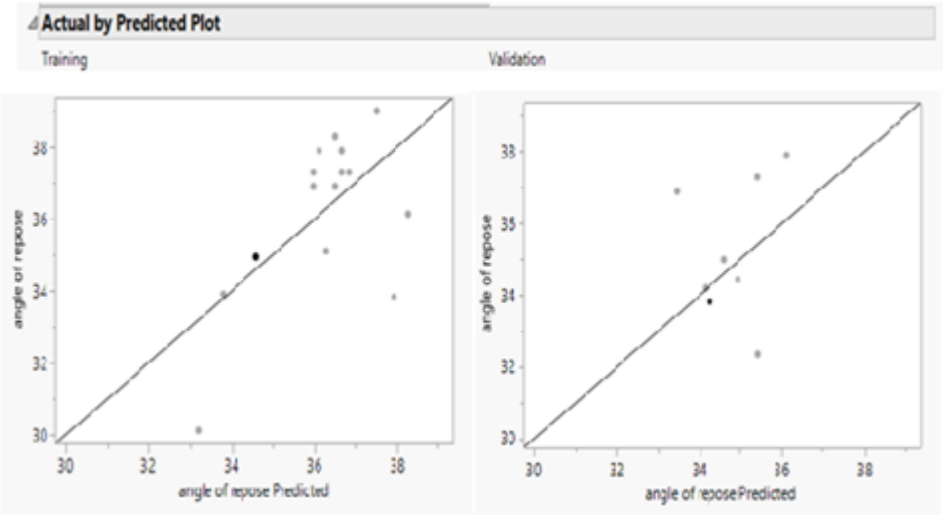

Fig. 7. Actual vs predicted angle of repose given by JMP software

3.3.3. Simulation of the ANN Network

The same data set recommended by the D-optimal design was used as the input for the ANN throughout the simulation of the created network. The concentrations of nonvolatile solvent and carrier:coating material were 25 and 20 respectively. For the simulation data set, the expected output sizes were 85.77 and 34.93 for the percentage drug release and angle of repose, respectively. The identical composition batch produced actual readings of 86.23 and 36.08, respectively [35].

3.4. Comparison of D-optimal design and ANN

The R^2 value for the D-optimal design-based quadratic model for the percentage drug release was 0.914, whereas for ANN, it was 0.943. The MSE for the D-optimal design-based quadratic model was 90.76, whereas for ANN, it was only 2.392. The R^2 value for the optimal design-based D-optimal design-based quadratic model for the angle of repose was 0.723, whereas for ANN, it was 0.751. The MSE for the D-optimal design-based quadratic model was 28.11, whereas for ANN, it was 11.04 [36].

3.5. Fourier transform infrared spectroscopy study

Any interaction between the drug and excipients was determined using FTIR studies. The FTIR spectra of DE and DE Liquisolid are illustrated in Fig. 8. Pure drug (Fig. 8(A)) showed characteristic peaks at 1731.45 cm^{-1} which was related to carbonyl (C=O) group stretching, 2857.73 cm^{-1} is related to alkane (C-H) group stretching, and 3246.32 cm^{-1} is related to amine (N=H) vibration group. In FTIR of DE Liquisolid (Fig. 8(B)), peaks were observed at 1645.42.cm^{-1}, 2872.78 cm^{-1}, and 3410.12 cm^{-1} with less intensity [37]. There is no shifting in peaks which indicates the absence of interaction between drug and excipients.

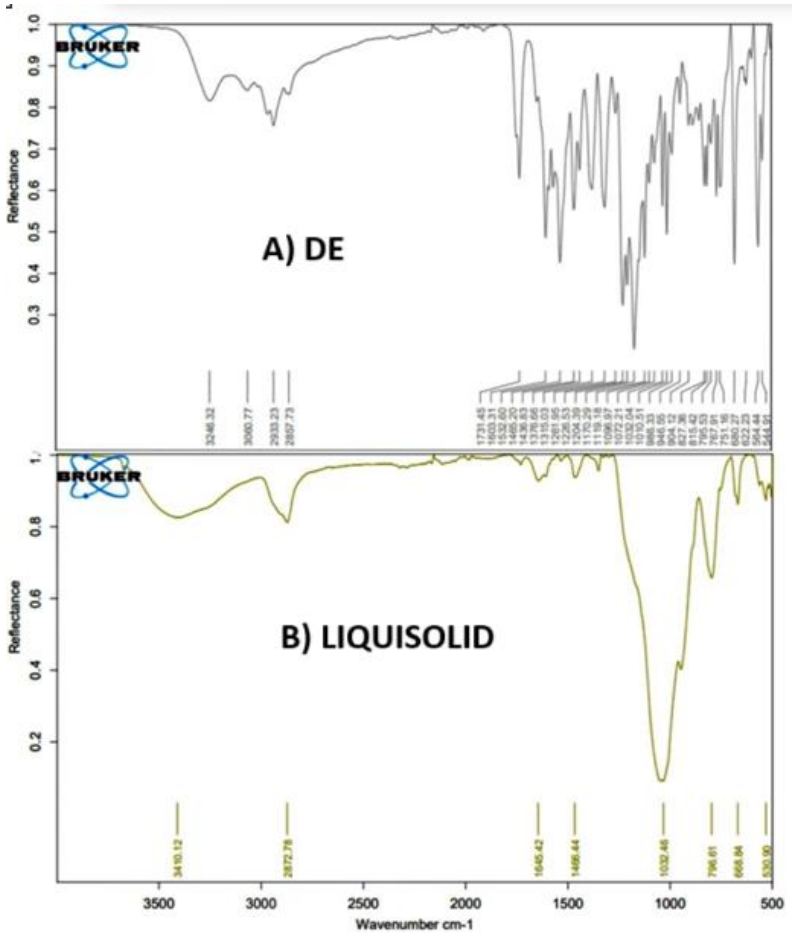

Fig. 8. FTIR of A) Dabigatran etexilate and B) Liquisolid capsule

3.6. X-ray diffraction study

XRD analysis was used to study the physical state of dabigatran etexilate in liquisolid state. Dabigatran etexilate's XRD pattern as seen in (Fig. 9(A)), reveals strong peaks at 2θ = 8.494°, 2θ = 13.3839°, 2θ = 15.706°, 2θ = 17.6642°, 2θ = 19.6472°and 2θ = 21.1395° with intensities 4624, 4985, 5043, 15295, 9667 and 12831, respectively, indicating the drugs crystalline nature. The XRD patterns of liquisolid capsule as illustrated in Fig. 9(A) are distinguished by diffuse spectra with intensities 273, 735, 738, 1585, 1769, and 2067 which are significantly less than the counts of the pure drug at the same 2θ values. The absence of prominent peaks suggests that the formulation is amorphous. The findings imply that in liquisolid form, dabigatran etexilate loses its crystallinity [38].

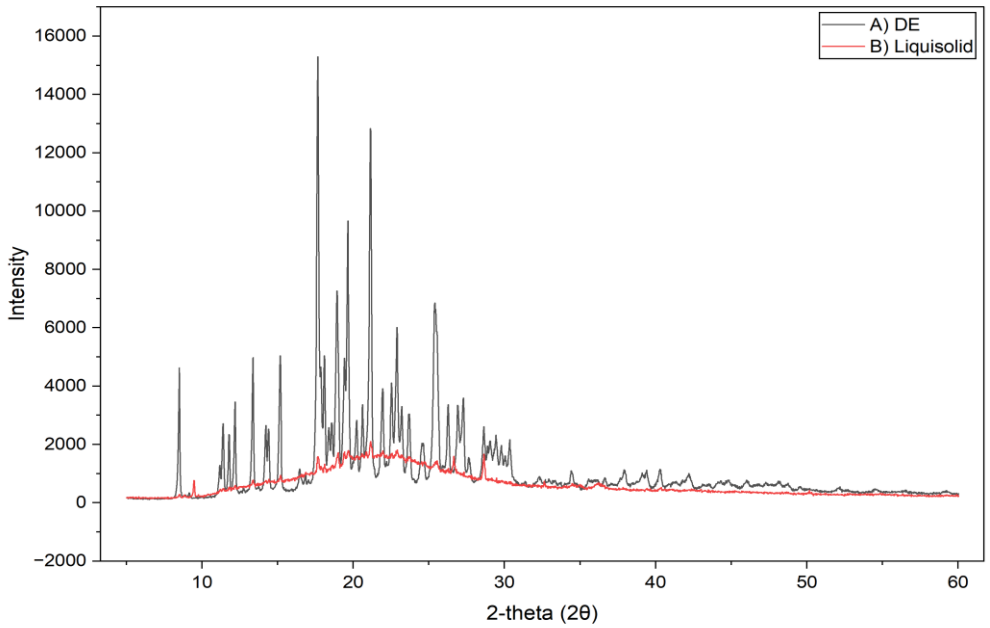

Fig. 9. XRD of A) Dabigatran etexilate and B) liquisolid capsule

4. Discussion

This work described the development of DE liquisolid capsules using the design of experiments approach and comparing it with the artificial neural network. One of dabigatran's prodrugs, dabigatran etexilate, is used as an anticoagulant. It is a better medication than warfarin, another anticoagulant, because of its quicker action, broader therapeutic window, and superior clinical efficacy. This weak basic drug's pH-dependent solubility reduces absorption, which lowers bioavailability and restricts use. Many methods have been used to increase the solubility of DE; one of the most successful strategies for increasing the solubility of poorly soluble medications is liquisolid technology. Both absorption and adsorption occur when the medicine contained in the liquid vehicle is integrated into a carrier material that has a porous surface and closely matted fiber inside. The inside surface of the particle captures the liquid that was first absorbed into its interior. Following saturation, the liquid is adsorbed onto the porous carrier particle's exterior and interior surfaces. The coating material's high adsorptive qualities and vast surface area then give the liquisolid system the desired flow property. There is only one reported work on the solubility enhancement of DE mesylate by liquisolid technology. The present study, however, sought to compare the prediction power of the D-optimal design and JMP for the dependent variables and improve the Liquisolid formulation of DE using the D-optimal design. The most common application of response surface methodology (RSM), an experiment-based statistical technique, is formulation optimization. In contrast to screening designs, which only allow data to be fitted into linear models, RSM allows data to be fitted into cubic, quadratic, and linear models. Nevertheless, RSM's dependent variables' capacity for prediction is insufficient. Another method for predicting dependent variables is to employ artificial neural networks, a form of artificial intelligence. By applying data training, it is possible to determine the link between independent variables. Responses are predicted by the training neural network using the data from the RSM designs' runs as input data.

Kolliphor EL and PEG 400 showed the highest solubility of the drug. When a nonvolatile solvent showed the greatest potential for solubilizing the medication, the higher is the amount of molecularly dispersed drug in the nonvolatile solvent and thereby an increase in the dissolution rate [39]. With percentage drug release (Y1) and angle of repose (Y2) as dependent factors and drug : nonvolatile solvent ratio (X1 25–50%), carrier : coating ratio (X2 - 10–30%), type of nonvolatile solvent (X3 - PEG 400/Kolliphor El), and type of carrier (X4 - Neusiln/Fujicalin) as independent variables, the D-optimal design was selected. ANOVA was used to confirm the statistical significance of the estimated parameters, and the D-optimal yielded 23 runs. The R^2 score for the ANN was 0.943, whereas the R^2 value for the D-optimal design-based quadratic model for drug release % was 0.914. The MSE for the ANN was only 2.392, while the MSE for the D-optimal design-based quadratic model was 90.76. While the R^2 value for ANN was 0.751, it was 0.723 for the optimal design-based D-optimal design-based quadratic model for angle of repose. The ANN's MSE was 11.04, whereas the D optimum design-based quadratic model's was 28.11. ANN's greater R^2 value suggests that it has more prediction power than D-optimal design. The optimized formulation contains PEG 400 as the nonvolatile solvent and Neusilin as a carrier. This is because an increase in dissolution was observed in liquisolid capsules when compared to Kolliphor EL as the drug was molecularly dispersed in PEG 400. PEG 400 increases the wetting of drug particles by reducing the interfacial tension between the drug particles and the dissolution medium. According to the "Noyes-Whitney" equation, the presence of PEG 400 surrounding the drug particles has helped to dissolve more drug in the stagnant diffusion layer, resulting in a higher concentration gradient and better drug dissolution. PEG 400 functions as a bridge between the drug particles and the dissolution medium, promoting easy diffusion of drug molecules from the dissolving surface [40]. Neusilin's higher capacity for liquid adsorption has resulted in improved flow properties in formulations. There is a decrease in the angle of repose values with an increase in the R-value. This might be due to the concentration of Aerosil 200 being higher in formulations with R = 10 and lower in formulations with R = 30 [41]. Aerosil is used as a coating material as it covers the irregularities present on the surface of granules and thereby increasing the flow properties of granules. However high increments in Aerosil 200 concentration decrease the flow properties of granules [42]. After creating the ideal formulation with a desirability value of 1, the percentage drug release and angle of repose were determined to be 86.23 ± 1.37 and 34.9329 ± 0.63, respectively. FTIR and XRD were used to assess the optimized formulation. FTIR analyses showed that there was no interaction between the medication and the excipients. XRD analyses showed that the drug's crystallinity had decreased.

5. Conclusions

This study describes the successful preparation and optimization of dabigatran liquisolid capsules. Dabigatran's limited bioavailability is due to its poor solubility and slow rate of dissolution. Dabigatran liquisolid capsules accelerated the dissolving process. The formulation was optimized using D-optimal design and artificial neural networks (ANN). The D-optimal design generated contour plots and 3D graphs that depicted the interaction of input and output data. Compared to the optimal design-based model, which had low MSE values and high R-values, the constructed and validated ANN model showed better predictability and accuracy. The study's result underlines the importance of properly selecting an optimization technique when adding desired features to a formulation. The current study proved liquisolid technique as a potential approach to enhance the dissolution of DE and the application of DoE and ANN in the optimization of liquisolid capsule formulations.

Author Contributions: Rama Devi Korni: Conceptualization, reviewing & editing. Thanmaisree Bora and Akhil Majji: Methodology and writing. Jagadeesh Panda: Conceptualization. Sre Meghna Killana: Methodology and editing.

Funding: This research received no external funding.

Acknowledgments: Our sincere gratitude to the Chairman, Sri Raghu Kalidindi, Raghu Educational Institutions, Visakhapatnam for his invaluable support and the facilities provided.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Blair, H.A.; Keating, G.M. Dabigatran Etexilate: A review in nonvalvular atrial fibrillation. *Drugs* **2017,** 77(3), 331-344. DOI: 10.1007/s40265-017-0699-z

2. Veenu, P.M.; Krutik,. K.S. Enhanced oral bioavailability and anticoagulant activity of dabigatran etexilate by self-micro emulsifying drug delivery system: systematic development, In vitro, Ex vivo and In vivo evaluation. *J. Nanomed. Nanotechnol*. **2018**, 9(01), Art. No: 480. DOI: 10.4172/2157-7439.1000480

3. Ge, L.; He, X.; Zhang, Y; Chai, F.; Jiang, L.; Webster, T.J.; Zheng, C. A dabigatran etexilate phospholipid complex nanoemulsion system for further oral bioavailability by reducing drug-leakage in the gastrointestinal tract. *Nanomedicine* **2017**, *30(17),* 30156-30159. DOI: 10.1016/j.nano.2017.08.009

4. Hu, M.; Zhang, J; Ding, R.; Fu, Y; Gong, T.; Zhang, Z. Improved oral bioavailability and therapeutic efficacy of dabigatran etexilate via Soluplus-TPGS binary mixed micelles system. *Drug Dev. Ind. Pharmy*. **2017**, *43(4),* 687–697. DOI: 10.1080/03639045.2016.1278015

5. Jagtap, S.; Magdum, C.; Jadge, D.; Jagtap, R. Solubility enhancement technique: a review. *J. Pharm. Sci. Res*. **2018**, *10(9*), 2205-2211.

6. Brahmankar, D.M.; Jaiswal, S.B. Biopharmaceutics and Pharmacokinetics: A Treatise. Vallabh Prakashan, Delhi, **2002**.

7. Panda, S.; Varaprasad, R.; Priyanka, K.; Swain, R.P. Liquisolid technique: a novel approach for dosage form design. *Int. J. Appl. Pharm*. **2017**, *9(3),* Art. No: 8. DOI: 10.22159/ijap.2017v9i3.18698

8. Lu, M.; Xing, H.; Jiang, J.; Chen, X.; Yang, T.; Wang, D.; Ding, P. Liquisolid technique and its applications in pharmaceutics. *Asian. J. Pharm. Sci*. **2017**, *12(2*), 115-123. DOI: 10.1016/j.ajps.2016.09.007

9. Kulkarni, A.; Alookar, N.; Mane, M.; Gaja, J. Liquisolid systems: a review. *Int. J. Pharm. Sci. Nanotech*. **2010**, *3(1),* 795-802. DOI: 10.37285/ijpsn.2010.3.1.1

10. Walke, P.S.; Pawar, A.Y.; Sonawane, D.D.; Bhamber, R.S. Liquisolid: a novel technique to enhance solubility and dissolution rate of BSC class II pharmaceuticals. *J. Pharm Res*. **2011**, *4(11),* 4011-4040. DOI: 10.24327/ijrsr.2022.1312.0562

11. Javadzadeh, Y.; Jafari-Navimipour, B.; Nokhodchi, A. Liquisolid technique for dissolution rate enhancement of a high dose water insoluble drug (carbamazepine). *Int. J. Pharm*. **2007**, *341(1-2*), 26-34. DOI: 10.1016/j.ijpharm.2007.03.034

12. Prasanthi, D.; Priyanka, K. Formulation and evaluation of liquisolid compacts of Dabigatran Etexilate Mesylate. *Indo Am. J. P. Sci*. **2018**, *05(01),* 572-583. DOI: 10.5281/zenodo.1164135

13. Kulkarni, A.S.; Aloorkar, N.H.; Mane, M.S.; Gaja, J.B. Liquiosolid system: a review. *Int. J. Pharm. Sci. Nanotechnol*. **2010**, *3(1),* 795-802. DOI: 10.37285/ijpsn.2010.3.1.1

14. Spireas, S.; Bolton, S. Sustained-release "liquisolid compacts". *Proc. Int. Symp. Control. Rel. Bioact. Mater*. **1998**, 25, 138-139.

15. Patel, B.B.; Shah, C.N.; Shah, R.M.; Shah, D.P. Liquisolid technology: a novel approach to enhance solubility of poorly water soluble drugs. *Res. J. Pharm. Technol*. **2015**, 8(12), 1733-1739. DOI: 10.5958/0974-360X.2015.00311.X

16. Bhattacharya, S. Design and development of Docetaxel solid self-microemulsifying drug delivery system using principal component analysis and D-Optimal design. *Asian J. Pharm*. **2018**, 12(01). DOI: 10.22377/ajp.v12i01.2051

17. Patel, D.S.; Pipaliya, R.M.; Surti, N. Liquisolid tablets for dissolution enhancement of a hypolipidemic drug. *Indian J. Pharm. Sci*. **2015**, *77(3),* 290-298 DOI: 10.4103/0250-474x.159618

18. Rodriguez-Granrose, D.; Jones, A.; Loftus, H.; Tandeski, T.; Heaton, W.; Foley, K.T.; Silverman, L. Design of experiment (DOE) applied to artificial neural network architecture enables rapid bioprocess improvement. *Bioprocess Biosyst. Eng*. **2021**, *44(6),* 1301-1308. DOI: 10.1007/s00449-021-02529-3

19. Olgac, A.; Karlik, B. Performance analysis of various activation functions in generalized MLP architectures of neural networks. *Int. J. Artif. Intell. Expert Syst*. **2011**, *1,* 111–122.

20. Baharin, A.; Abdullah, A.; Yousof, S.N.M. Prediction of bioprocess production using deep neural network method. *Telkomnika* **2017**, *15*, 805–813.

21. Elkordy, A.A; Tan, X.N; Essa, E.A. Spironolactone release from liquisolid formulations prepared with Capryol™ 90, Solutol® HS-15 and Kollicoat® SR 30 D as non-volatile liquid vehicles. *Eur. J. Pharm. Biopharm*. **2013**, *83(2),* 203-223. DOI: 10.1016/j.ejpb.2012.08.004

22. Tayel, S.A; Soliman, II.; Louis, D. Improvement of dissolution properties of carbamazepine through application of the liquisolid tablet technique. *Eur. J. Pharm. Biopharm*. **2008**, 69, 342–347. DOI: 10.1016/j.ejpb.2007.09.003

23. Salunkhe, A.; Yadav, A.; Adhikrao; Sakhare, S.; Doijad, R.; Shete, A. Neusilin based liquisolid compacts of albendazole: design, development, characterization and in vitro anthelmintic activity. *J. Res. Pharm*. **2019**, *23(3),* 441-456. DOI: 10.12991/jrp.2019.151

24. Vinod Valjibhai Siju, Moinuddin Soniwala. Liquisolid compact: A new technology for optimization of paliperidone tablets by central composite design. *Int. J. Pharm. Sci*. Rev. **2017**, *45(1),* 11-17.

25. Fahmy, R.H.; Kassem, M.A. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm*. **2008,** *69(3),* 993-1003. DOI: 10.1016/j.ejpb.2008.02.017

26. Burra, S.; Yamsani, M.; Vobalaboina, V. The Liquisolid technique: an overview. *Brazilian J. Pharm. Sci*. **2011**, *47(3),* 475–482. DOI: 10.1590/S1984-82502011000300005

28. Hentzschel, C.M.; Sakmann, A.; Leopold, C.S. Suitability of various excipients as carrier and coating materials for liquisolid compacts. *Drug Dev. Ind. Pharm*. **2011**, *37(10),* 1200–1207. DOI: 10.3109/03639045.2011.564184

29. Spireas, S. Liquisolid systems and methods of preparing same. **2002**, U.S Patent 6423339B1.

30. Prajapati, S.T.; Bulchandani, H.H.; Patel, D.M.; Dumaniya, S.K.; Patel, C.N. Formulation and evaluation of liquisolid compacts for olmesartan medoxomil. *J. Drug Del*. **2013**, *2013*, Art. No: 870579. DOI: 10.1155/2013/870579

31. Valaei, I.; Hassan-Beygi, S.R.; Kianmehr, M.H.; Massah, J. Investigation of avalanche time and Carr's index of poultry litter powder as flowability indices. *Cercetari Agronomice in Moldova*. **2012**, XIV, *4(152),* 15-27. DOI: 10.2478/v10298-012-0061-2

32. Brown, C.K.; Friedel, H.D.; Barker, A.R.; Buhse, L.F.; Keitel, S.; Cecil, T.L.; Kraemer, J; Morris, J.M.; Reppas, C.; Stickelmeyer, M.P.; Yomota, C; Shah, V.P. FIP/AAPS joint workshop report: dissolution/in vitro release testing of novel/special dosage forms. *AAPS PharmSciTech*. **2011**, *12(2),* 782-94. DOI: 10.1208/s12249-011-9634-x

33. Chella, N.; Shastri, N.; Tadikonda, R.R. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. *Acta Pharm. Sinica B*. **2012**, *2(5),* 502–508. DOI: 10.1016/j.apsb.2012.07.005

34. Aghajanpour, S.; Yousefi Jordehi, S.; Farmoudeh, A.; et al. Applying liquisolid technique to enhance curcumin solubility: a central composite design study. *Chem. Pap*. **2024**, *78*, 9257–9271. DOI: 10.1007/s11696-024-03741-7

35. Dhanaraju; M. D.; Devendiran; S.; Vadaga; A.; Ramya; N. Formulation and optimization of liquisolid compact of Atazanavir by using DoE approach. *Eur. J. Pharm.* **2023**, *12*, 53-66. DOI: 10.48047/ecb/2023.12.si11.0032023.15/07/2023

36. Saini, L.M.; Soni, M.K. Artificial neural network based peak load forecasting using levenberg–marquardt and quasi-newton methods. *IEE Proceedings - Generation, Transmission and distribution*. **2002**, *149(5),* 578. DOI: 10.1049/ip-gtd:20020462

37. Mourabet, M.; Abdelhadi; El Rhilassi, l.; Bennani-Ziatni, M.; Taitai, A.. Comparative study of artificial neural network and response surface methodology for modelling and optimization the adsorption capacity of fluoride onto apatitic tricalcium phosphate. *Univers. J. Appl. Math*. **2014**, *2(2),* 84-91. DOI: 10.13189/ujam.2014.020202.

38. Sari, D.W.; Wardhana, Y.W.; Rusdiana, T. Enhancement of solubility BCS class II and IV pharmaceuticals by liqusolid technique: A review. *Indo. J. Pharm*. **2020,** *2(2),* 77-88. DOI: 10.24198/idjp.v2i2.27297

39. Amrani, F.; Secretan, P.-H.; Sadou-Yayé, H.; Aymes-Chodur, C.; Bernard, M.; Solgadi, A.; Yagoubi, N.; Do, B. Identification of dabigatran etexilate major degradation pathways by liquid chromatography coupled to multi stage high-resolution mass spectrometry. *RSC Adv*. **2015**, *5,* 45068-45081. DOI: 10.1039/C5RA04251H.

40. Korni, R.D.; Gonugunta, C.S. Olanzapine liquisolid tablets using Kolliphor EL with improved flowability and bioavailability: In vitro and In vivo characterization. *Turkish J. Pharm. Sci*. **2024**, *21(1*), 52-61.

41. Jaydip, B.; Dhaval, M.; Soniwala, M.M.; Chavda, J. Formulation and optimization of liquisolid compact for enhancing dissolution properties of efavirenz by using DoE approach. *Saudi Pharm. J.* **2020**, 28(6), 737-745. DOI: 10.1016/j.jsps.2020.04.016

42. Korni, R.; Voodikala, S.; Gonugunta, C.S.; Jayanti, V. Liquisolid technique: An approach to enhance the dissolution rate of Olanzapine. *Indian J. Pharm. Sci*. **2018**, *80(6),* 1003-1010.

43. Shah, P.; Desai, H.; Vyas, B.; Lalan, M.; Kulkarni, M. Quality-by-design-based development of Rivaroxaban-loaded liquisolid compact tablets with improved biopharmaceutical attributes. *AAPS PharmSciTech*. **2023**, *24,* Art. No: 176. DOI: 10.1208/s12249-023-02635-3