



OPEN RSM and AI based machine learning for quality by design development of rivaroxaban push-pull osmotic tablets and its PBPK modeling

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The study is based on applying Artificial Neural Network (ANN) based machine learning and Response Surface Methodology (RSM) as simultaneous bivariate approaches in developing controlled-release rivaroxaban (RVX) osmotic tablets. The influence of different types of polyethylene oxide, osmotic agents, coating membrane thickness, and orifice diameter on RVX release profiles was investigated. After obtaining the trial formulation data sets from Central Composite Design (CCD), an ANN-based model was trained to get the optimized formulations. The Physiological-based Pharmacokinetic (PBPK) modeling of the predicted formulation was performed by GastroPlus™ to simulate in vivo plasma profiles under fasting and fed conditions. In vitro release tests showed zero-order RVX release for up to 12 h. Using graphical and numerical methods, the predicted formulation generated by the prediction profiler was cross-validated by the CCD-based optimized formulation. Analysis of Variance (ANOVA) findings revealed no significant difference between the predicted and optimized formulations and these formulations have a shelf life of 22.47 and 17.87 months, respectively. The PBPK modeling of RVX push-pull osmotic pump (PPOP) tablets suggested enhanced bioavailability in the fasted (up to 82%) and fed (up to 98.5%) state compared to immediate-release tablets. The results indicated that ANN can be effectively used for osmotic systems due to their complex nature and nonlinear interactions between dependent and independent variables.

Keywords Rivaroxaban, Osmotic tablets, Artificial neural network, Quality by design, PBPK modeling, GastroPlus

Abbreviations

ANN	Artificial neural network
RSM	Response surface methodology
RVX	Rivaroxaban
CCD	Central composite design
ANOVA	Analysis of variance
PBPK	Physiologically based pharmacokinetic
PPOP	Push-pull osmotic pump
PE	Pulmonary embolism
DVT	Deep vein thrombosis
MI	Myocardial infarction
VTE	Venous thromboembolism
ODDSs	Osmotic drug delivery systems
EOP	Elementary osmotic pump
FDA	Food and drug administration
QbD	Quality by design
MLP	Multi-layer perceptron

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CYP	Cytochrome-P
Pgp	P-glycoprotein
PEO	polyethylene oxide
ACAT	Advanced compartment and transit
USP	United States pharmacopoeia
SLS	Sodium lauryl sulphate
DoE	Design of experiment
FTIR	Fourier transform infrared
DSC	Differential scanning calorimetry
SEM	Scanning electron microscope
AIC	Akaike information criterion
SC	Schwarz criterion
API	Active pharmaceutical ingredient
ICH	International Council for Harmonization

Thromboembolic diseases are a leading source of morbidity and mortality associated with some of the most severe health conditions, such as pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, and myocardial infarction (MI). Warfarin is the most widely used oral anticoagulant, with annual prescriptions typically equal to 0.5–1.5% of the population^{1,2}. Direct oral anticoagulants targeting the single coagulation factor (Xa or thrombin) have been developed in recent years to circumvent the limitations of traditional anticoagulants³. Rivaroxaban (RVX) is an oral, direct Factor Xa inhibitor that has been licensed in over 100 countries for the prevention and treatment of venous thromboembolism (VTE) after elective hip or knee replacement surgery, as well as stroke prevention in individuals with nonvalvular atrial fibrillation⁴. Several dosage strengths of rivaroxaban immediate-release tablets 2.5, 5, 10, and 20 mg have shown dose-dependent food effects. The highest dose strength tablet (20 mg) should be taken with food to achieve the favorable food effect for oral absorption and systemic availability, while the lower dose (10 mg or less) can be taken with or without food⁵. One approach to address the food effects on drug bioavailability is developing osmotically controlled drug delivery systems (ODDSs).

Osmotically controlled-release dosage formulations represent a significant advancement in drug delivery systems, offering distinct advantages over matrices and reservoir-based oral controlled-release systems. The osmotic pressure generated within the tablet's core serves as a driving force to control the drug release at a constant rate, independent of GI motility, pH, or food. Push-pull osmotic pump (PPOP) tablet systems consist of bilayer tablets, which are preferred over elementary osmotic pump (EOP) systems for achieving consistent and predictable drug release rates^{6,7}. One layer holds the drug and an osmotic agent, while the other contains an osmopolymer or a hydrophilic expansion polymer. The swelling of the push layer in an aqueous environment aids in the drug release at a zero-order rate and produces a driving force against the drug layer. The drug suspension produced in the drug layer then comes out through the orifice⁸. Numerous benefits are associated with these dosage forms, like constant drug levels at the site of action, no peak fluctuations, lesser dosing frequency, fewer side effects, and better patient compliance⁶.

Pharmaceutical companies are investing billions of dollars in fostering the development of high-quality products and drug discoveries. As the FDA assesses the application's process design's execution and efficacy and risk management for a successful technology transfer from the lab to the production level, Quality by Design (QbD) has become crucial for product approval⁹. QbD aims to improve understanding of pharmaceutical products and manufacturing processes. Developing pharmaceutical products based on the QbD-based methodology entails complete compliance with a well-defined roadmap¹⁰. On the other hand, artificial neural networks (ANNs) are an efficient multi-variate pharmaceutical formulation optimization tool that can be applied as an efficient alternative methodology for product development. The ANN computational model is a non-linear predictor regression model due to better predictive capacity¹¹. Multi-layer perception (MLP) models are among the most successful types of ANNs, with a fully connected network consisting of one or more layers built from datasets. Still, many ANN models are mostly built with one hidden layer and minimum numbers of input variables to avoid confounding¹². Software like CAD/Chem, INForm, JMP-Pro, MATLAB, etc., are used to build ANN models for developing pharmaceutical products.

Physiologically based pharmacokinetic (PBPK) modeling is a predictive tool and used for analyzing and assessing pharmacokinetic data. Depending on the intended use and the degree of knowledge regarding the drug's properties, PBPK models can include different levels of physiological complexity and drug disposition and elimination processes¹³. The clinical pharmacokinetic studies of RVX show significant inter-individual variability, most likely due to its numerous elimination routes¹⁴, variable mechanism of metabolism (breakdown by CYP3A4), and P-glycoprotein (Pgp)-dependent efflux¹⁵. CYP superfamily is the most abundant and critical enzyme family, responsible for over 75% of drug metabolism in humans¹⁶. The complex pharmacokinetics of RVX can be predicted by PBPK modeling without intensive in vivo studies, and only physicochemical, physiological, and formulation factors are considered when building a PBPK model. PBPK models provide a rational basis for data integration and can predict both the extent and rate of uptake¹⁷. Softwares such Kinetica, Phoenix, Symcyp, GastroPlus, etc., are the most reported for predicting pharmacokinetic profiles from in vitro dissolution data by integrating various physiological and drug-related parameters and simulating different demographic groups^{18,19}.

The present work describes the simultaneous application of Artificial Neural Network (ANN) and Central Composite Design (CCD)-based Response Surface Methodology (RSM) techniques as multivariate systematic approaches for developing a robust and reproducible methodology for designing and optimizing push-pull osmotic tablets of RVX, a poorly soluble BCS class II drug with moderate inter-personal pharmacokinetic variability²⁰. The input variables, like type and concentration of polyethylene oxides (PEOs), osmogen amount

(sodium chloride), drug loading capacity, coating weight gain, and orifice size, were initially screened and optimized by numerical and graphical techniques. Finally, the developed ANN model was used to generate a prediction profiler. The application of ACAT (Advanced Compartmental and Transit) based developed and optimized PBPK model using GastroPlus™ was also demonstrated as a predictive tool for obtaining the in vivo pharmacokinetic profile of the optimized formulation (F_{pred}). The current work aimed to develop an interpretable bivariate approach using ANNs and QbD in any data-rich production step i.e. from the formulation design to the quality assurance of the final dosage form in line with Gastroplus™ as a well-established PBPK modeling tool.

Materials and methodology

Materials and chemicals

Rivaroxaban was gifted from Searle Pharmaceuticals (Karachi, Pakistan). Opadry® CA and PEOs (WSR N-10 NF, WSR N-750 NF, WSR N-80 NF, WSR-301 NF, WSR-303 LEO, and WSR Coagulant) were kindly provided by Colorcon Limited (Kent, United Kingdom). Avicel™ PH-101, Aerosil™ 200, and Magnesium Stearate were purchased from FMC Corporation (United States). Sodium Hydroxide, Potassium dihydrogen Phosphate, sodium chloride, Acetonitrile, Methanol, and hydrochloric acid [37–38% w/w] were purchased from Merck (Germany). All other chemicals utilized during the study were of analytical grade.

Screening of formulation parameters to develop Rivaroxaban PPOP tablets

The initial screening of formulation variables like the concentration and grade of Polyethylene oxide (PEO), sodium chloride (NaCl) amount, coating weight gain percent, and orifice diameter, was performed in both the layers (push and pull) to identify their suitability for developing PPOP tablets. The effect of drug amount (5, 15, and 30 mg) was also assessed to study the impact of varying levels of the formulation factors on drug release percent. The input factors were tested at three levels (see Table 1).

Compression of core tablets

For the pull layer, calculated amounts of RVX, PEO, NaCl, Avicel, and magnesium stearate were sieved separately through Mesh # 60. All the powders except magnesium stearate were mixed with the tumbling action for 5–6 min. Magnesium stearate was later added and further blended for 3 min. A similar method was applied to push layer ingredients, which contained iron oxide as a colorant for identification. The powder blend was compressed into bilayer tablets by double compression method: the initial pre-compression of the drug layer under 0.5 ± 0.15 kN was followed by the final compression of the push layer under 6.0 ± 0.55 kN with a target compression weight of 450 mg using biconcave punches using a benchtop tablet press-Natoli NP-RD10A (Natoli Engineering Inc. MO, USA)²¹.

Coating and drilling of tablets

A commercially available Opadry® CA coating system was applied following a 24-hour resting period to provide elastic stress relaxation to create a semi-permeable membrane on the tablets. Acetone and water in a ratio of 9:1 by weight were used to make the coating solution, which contained 7% w/w amount of Opadry® CA²². The compressed tablets were then coated using a traditional tablet coating pan that was rotated 3–6 rotations per minute. The inlet and outlet air temperatures were kept at approximately 45 °C and 28 °C, respectively^{23,24}. The coating solution was then sprayed at a rate of 4–5 ml/min, the automation pressure was adjusted to 1 kg/cm², and the coating pan speed was increased to 18–24 rpm²⁵. The coated tablets were kept for drying overnight in a hot air oven at 50 °C for 16 h after the required coating weight gain was reached. The drug-containing side of the tablet was drilled through in the center using a micro-drilling bit measuring between 0.3 and 0.9 mm.

In-vitro drug release studies and statistical analysis

In-vitro drug release studies of all the trial batches were conducted using the USP Type-II apparatus (Erweka DT600, GmbH, Huesenstamm, Germany). The tablets were tested in a 900 ml dissolution medium of acetate buffer pH 4.5 + 0.5% SLS²⁶ at the agitation speed of 75 rpm, and the medium temperature was maintained at 37 ± 0.5 °C. A sample of 10 ml was drawn at pre-determined time intervals (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h) and filtered through a 0.45 µm filter to make the working strength equivalent to 0.01 mg/ml. The cumulative percentage of drug release was determined using a UV-spectrophotometer (UV-1800, Shimadzu Corporation, Kyoto, Japan) at 248 nm²⁷. Equal volumes of fresh medium were replaced after every sampling. The dissolution profiles were compared using the similarity factor (f_2) test (ref) according to the given equation:

$$f_2 = 50 * \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

Where R_i and T_i are, respectively, the release from reference and test samples at time intervals, and t and n are the number of samples analyzed. The effect of input factors on percentage drug release was considered significant if the two profiles exhibited the f_2 value below 50²⁸.

Experimental design for rivaroxaban PPOP tablets

Central Composite Design (CCD), a meticulously chosen tool in the formulation optimization process, was employed to statistically analyze critical factors at a minimum of three levels. The Design of Experiment (DoE) was obtained by Design Expert® version 13 (Stat Ease, Inc, Minneapolis MN 55413, USA), keeping the amount of PEO in the push layer (40–80 mg), NaCl amount in the drug layer (20–50 mg), and coating weight gain (4–12%) as the independent variables (X_1 – X_3). Twenty trial runs i.e. 8 factorial points, 6 central points, and 6

Formulation code	Drug layer				Push layer				Coating			
	PEO type (kDa)	PEO amount (mg)	NaCl amount (mg)	Drug amount (mg)	Mg. Stearate (mg)	PEO type (kDa)	PEO amount (mg)	NaCl amount (mg)	Mg. Stearate (mg)	Fe ₂ O ₃ (mg)	Coating weight gain (%)	Orifice diameter (mm)
F1-F3	WSRN-10 (100), WSR N-80 (200), WSRN-750 (300)	200	35	30	3	WSR Coagulant (5000)	60	35	1	1	8	0.6
F4-F6		200, 250, 300	35	30	3	WSR Coagulant (5000)	60	35	1	1	8	0.6
F7-F9		200	20, 35, 50	30	3	WSR Coagulant (5000)	60	35	1	1	8	0.6
F10-F12		200	35	5, 15, 30	3	WSR Coagulant (5000)	60	35	1	1	8	0.6
F13-F15	WSRN-80 (200)	200	35	30	3	WR 301 (4000), WSR Coagulant (5000), 303 WSR (7000)	60	35	1	1	8	0.6
F16-F18	WSRN-80 (200)	200	35	30	3	WSR Coagulant (5000)	40, 60, 80	35	1	1	8	0.6
F19-F21	WSRN-80 (200)	200	35	30	3	WSR Coagulant (5000)	60	20, 35, 50	1	1	8	0.6
F22-F24	WSRN-80 (200)	200	35	30	3	WSR Coagulant (5000)	60	35	1	1	4, 8, 12	0.6
F25-F27	WSRN-80 (200)	200	35	30	3	WSR Coagulant (5000)	60	35	1	1	8	0.3, 0.6, 0.9

Table 1. Tablet parameters and levels used in the screening of rivaroxaban PPOP tablets.

axial points (F1–F20) were observed for the critical output variables, i.e., % drug release at 2, 6 and 12 h (Y_1 – Y_3) and zero-order rate constant (Y_4 ; RSQ_{zero}). The data sets of the 20 trial formulations obtained from CCD were utilized to train the ANN model and get the predicted quantities of the input variables (X_1 – X_3) to obtain the targeted critical responses (Y_1 – Y_4).

Pre-compression assessment of API and blends

To examine the flow characteristics of the trial powder blends, the pre-formulation assessment of trial batches, including bulk and tapped densities, Carr's index or compressibility index, Hausner's ratio, and angle of repose was carried out per pharmacopeial specifications^{29,30}. After adding the known quantity of powder blends to a 10-ml measuring cylinder, bulk density was calculated. After mechanically tapping the graduated vessel until the volume decrement was constant, the tapped density was measured. The parameters were calculated using the following equations:

$$\rho_{bulk} = \text{Mass of sample (g)} / \text{bulk volume (ml)} \quad (2)$$

$$\rho_{tapped} = \text{Mass of sample (g)} / \text{tapped volume (ml)} \quad (3)$$

Where ρ_{bulk} the bulk density, and bulk volume is the initial powder blend volume in the cylinder.

$$\text{Carr's index} = (\rho_{tapped} - \rho_{bulk} / \rho_{tapped}) * 100 \quad (4)$$

$$\text{Hausner's Ratio (HR)} = \rho_{tapped} / \rho_{bulk} \quad (5)$$

Powder material was passed through a funnel that measured 9.5 cm in height and had an internal orifice diameter of 1.8 cm and an upper spout diameter of 7.2 cm to calculate the angle of repose. The funnel was set up on the workbench, mounted roughly at 20 cm height from the Petri dish's base. After the material was put into the funnel with the spout plugged, it was allowed to pass through the opening and gathered in a petri dish. A sliding vernier caliper measured the cone's height (h) and diameter (d) three times³¹. The angle of repose was computed using the mean values of "d" and "h" according to the formula:

$$\tan \theta = 2h/d \quad (6)$$

Compression and coating of the designed formulations

All the designed batches (F1–F20) were directly compressed into bilayer tablets using the double compression method, as explained in the previous section. The coating procedure and conditions were identical, as described in earlier sections. The formulations were then drilled by a micro-drill machine (Proxxon MF 70, Germany) to create the optimum orifice of 0.6 mm.

Compatibility studies by FTIR and DSC analysis

The drug-excipient interaction was evaluated by Fourier transform infrared (FTIR) spectroscopy (Nicolet-6700; Thermo Scientific, United States). The spectra of the pure drug and powder excipients individually were generated in the 4000–400 cm^{-1} range. Similarly, the center point formulation tablet was crushed in a mortar and pestle and analyzed to identify any post-compression interaction. The samples were then examined at an accelerating voltage of 20 kV. Finally, the IR spectra of the pure drug and samples were compared³².

Differential scanning calorimetric (DSC 250, TA Instruments, DE, USA) analysis was carried out for pure rivaroxaban, individual excipients (microcrystalline cellulose, PEO, NaCl, and magnesium stearate), and a drug-excipient mixture from crushed tablets (center point formulation). The 2–8 mg samples were hermetically sealed and kept at the temperature range of 40–400 °C at the heating rate of 10 °C min^{-1} . Standard Indium was used to calibrate the instrument at the Nitrogen purging rate of 50–100 ml/min. The data acquisition and subsequent calculations were performed using TRIOS software (TA Instruments, New Castle, DE, USA). The overlay thermograms were constructed using MS PowerPoint 365 (Microsoft Corp. USA) and were observed for any interaction³³.

Pharmaceutical quality evaluation of tablets

All the coated and core tablets of the trial batches were subjected to various pharmacopeial and non-pharmacopeial assessments ($n=20$), i.e., weight, thickness, and diameter variation tests using electronic weighing balance (Sartorius 224 S, Germany) and digital vernier caliper (Seiko brand, China). The mechanical strength of the core tablets was assessed by friability and hardness tests using Roche-type friabilitor (Erweka D2800, Huesenstamm, Germany) and Dr. Schleuniger Pharmatron M50 MultiTest 50 (Pharmatron, Switzerland)³⁴.

Content uniformity test

The content uniformity test of all the trial formulations was performed using the HPLC method described by Effat Souiri et al.³⁵. The standard stock solution of rivaroxaban was prepared by dissolving 10 mg of the drug in a mixture (10 ml) of acetonitrile and methanol (85:15 v/v). The calibration curve was constructed for 50, 25, 15, 10, 5, 3, and $\mu\text{g/ml}^{-1}$ solutions, prepared in the mobile phase containing a mixture of KH_2PO_4 50 mM (pH 3.0) and acetonitrile (60:40, v/v). The mobile phase was filtered through a 0.45 μm membrane filter and degassed by ultrasonication before use. Chromatographic separation was performed through a C18 column (3.9 × 300 mm, Bondapak RP) at 25 °C using HPLC (LC-10 AT VP Shimadzu Japan). The rivaroxaban response was recorded at 249 nm using a UV detector (LC 10a VP, Shimadzu, Japan). The test solutions of each tablet ($n=10$) equivalent to 50 $\mu\text{g/ml}^{-1}$ were prepared, and the percentage drug content was calculated³⁶.

In vitro drug release studies and release kinetics studies

The in-vitro drug release was performed on all the designed formulations per the procedure explained in the previous section of dissolution testing. The drug release mechanism was examined using the dissolution profiles of each trial batch. Weibull, Higuchi, Korsmeyer Peppas, Hixon Crowell, and first-order kinetic models were among the models used to use DD Solver to analyze the kinetic mechanism of in-vitro drug release³⁷. The cumulative percent drug release at 2, 6, and 12 h (Y_1 – Y_3) was assessed to evaluate the effect of independent variables. The zero-order release constant (Y_4 ; RSQ_{Zero}) was also determined to evaluate the RVX release kinetics³⁸.

ANN-assisted development of rivaroxaban PPOP tablets

The current study used the Multilayer perceptrons (MLPs) based feed-forward back propagation method to train and test the ANN model to develop RVX-PPOP tablets using JMP® Pro 16 software (SAS Institute Inc. North Carolina, USA). The developed model was later cross-validated using the most established numerical and graphical optimization techniques. The CCD-generated data (Y_1 – Y_4) of the trial formulations was prepared in replicates of ten and was applied for the supervised training of the ANN model by the Holdback input randomization method. The data set was divided into a ratio of 70:30 for the training and testing model³⁹. Since the ANN model efficiency depends on the number of neural nodes in the hidden layer, the optimal number of the neural nodes was tested in the range of 3–7 by the activation function TanH (Tangent Hyperbolic). The neural node showing the value of r^2 closer to unity with the minimum sum of square errors (SSE) against each critical response (Y_1 – Y_4) was considered optimum and selected to generate the prediction profiler (predicted formulation variables)⁴⁰. The prediction and contour profilers were generated at the neural node exhibiting the maximum value of the coefficient of regression (node 5; $r^2 = 1$). The predicted formulation, F_{pred} was prepared, and all the critical response variables were determined.

Optimization based on the QbD approach

The Numerical and graphical optimization procedure using “Design Expert” software version 10 (Stat-Ease, Minneapolis, United States) was used to ascertain the formulation performance (F_{pred}) obtained by the developed ANN model. The technique was adopted to get the optimum amounts of X_1 – X_3 variables to achieve the desirable response factors (Y_1 – Y_4) within the targeted constraints. The targeted constraints were: <20% DR at 2 h, 40–60% DR at 6 h, >85% DR at 12 h, and 0.95–1 as RSQ_{zero} for the corresponding response factors Y_1 – Y_4 respectively. The individual and interactive effects of PEO, NaCl, and percentage weight gain after perturbation plots graphically and mathematically presented coating, 3D response surface curves, and polynomial model equations. For the individual responses, model fitness was evaluated by the ANOVA (analysis of variance), and “ $p < 0.05$ ” was considered significant. The model equations (polynomial) generated for each critical response variable were later used to get the optimized formulation F_{opt} based on the desirability function closer to unity. The ramp and overlay plots were constructed to present the optimum X_1 – X_3 for the targeted constraints (Y_1 – Y_4) and the generated design space⁴⁰.

Comparison of the optimized and predicted formulations by ANOVA

The trained ANN model was cross-validated by comparing the predicted formulation (F_{pred}) and the CCD-generated formulation (F_{opt}) obtained by numerical and graphical optimization approaches. The formulations were prepared in triplicates, and the drug release percentage (Y_1 – Y_3) was determined in dissolution medium pH 4.5 (acetate buffer; 0.5% sodium lauryl sulfate). The drug release data of the formulations were compared by ANOVA (analysis of variance), “F” was calculated, and a significant difference was considered at a 95% confidence interval ($p < 0.05$). The RSQ_{Zero} (Y_4) and the rest of the pharmaceutical attributes (weight thickness, diameter, Hardness variation, percentage friability, and content assay) were also determined⁴⁰.

Scanning electron microscopy analysis

The optimized formulation (F_{pred}) surface morphology was analyzed using the SEM study before and after the complete drug release. After mounting the SEM samples on aluminum studs, they were covered in 250 Å of gold coating. The coated tablets were carefully placed in a petri dish and dried at 50 °C for 12 h in a hot air oven following the completion of the 24-hour dissolution process, and then the scanning electron micrographs were obtained (JSM-6380 A, JEOL, Japan)⁴¹.

Accelerated stability studies

The optimized formulations were stored in airtight amber glass bottles. According to ICH guidelines, they were kept in the stability chamber (NuAire, Plymouth, MN, United States) at 40 ± 2 °C and $75 \pm 5\%$ relative humidity for 0, 1, 3, and 6 months under accelerated stability conditions. Using Minitab® 20 (Minitab, LLC, Pennsylvania, USA), shelf life was calculated after determining the percentage drug assay and all the critical parameters (Y_1 – Y_4)⁴².

PBPK modeling and simulation

Model building

The systemic disposition of rivaroxaban from the optimized formulation (F_{pred}) was predicted using the ‘Advanced Compartmental Absorption and Transit’ (ACAT®) model embedded in GastroPlus™ software version 9.9 (Simulations Plus Inc., Lancaster, CA, USA). Different formulation and physiological parameters (logP, blood: plasma ratio, pKa, unbound plasma fraction, effective permeability) obtained from the literature and ADMET™ predictor (Simulations Plus Inc., Lancaster, CA, USA) module were incorporated and depicted in Table 2^{5,43,44}. Due to the non-availability of intravenous plasma data in the literature, an oral 10 mg solution

plasma profile was used to deduct the drug disposition parameters like systemic clearance (Cl_{sys}), half-life ($T_{1/2}$), volume of distribution (V_d), and distribution constants between central and peripheral compartments. These pharmacokinetic parameters were obtained using an empirical model fitting in the PKPlus[®] module of GastroPlus[®] by employing 1, 2 and 3 compartments separately. The best-fitted compartmental model was selected based on the Akaike information criterion (AIC) and Schwarz criterion (SC), whereas the Hooke & Jeeves pattern search method was used, and the weighing was equal to $1/Yhat^2$. The obtained parameters were fixed and employed for further simulations⁵.

Model validation

The robustness and predictive power were initially evaluated by comparing the simulated plasma profile of 10 mg oral solution with the in vivo data obtained from the literature, followed by the verification of the developed model by simulating the in vivo profiles of the oral tablet (10 mg)⁴⁵. The model was then validated (based on r^2 values), and the calibration was performed based on the relative accuracy between predicted and observed PK parameters, which were compared by determining the percent predictive error and fold error according to the formulae⁴⁶:

$$FE = Predicted\ value / Observed\ value \tag{7}$$

Simulation of RVX PPOP tablets

Different inputs were added in the prediction process like the dissolution testing result of the optimized formulation in USP-defined biorelevant media for fasting and fed conditions and CR Gastric as the dosage form⁴⁷. The built model was used to simulate the PK profile of the optimized controlled-release formulation (30 mg) in both the fed and fasted states to assess the impact of food on the degree and extent of intrinsic absorption of RVX from the gut wall⁴⁸.

Results

Screening of formulation parameters on the drug layer of RVX-PPOP tablets

Three different types of PEOs were used in the same concentration (200 mg) with different molecular weights, 100k (N-10), 200k (N-80), and 300k (N-750) in formulations F1–F3 and drug release profiles were obtained as shown in Fig. 1a. On comparison, the f_2 values for N-10 and N-80 were 50.58, but no similarity was observed for N-80 and N-750 (f_2 ; 40.12) and N-750 and N-10 (f_2 ; 30.58); however, the lag time of 3 h and 1 h was observed with N-750 and N-80 that might be attributed to their high molecular weights, i.e., 200 K and 300 K respectively. The suitable amount of PEO N-80 was later evaluated for the concentrations of 200 mg, 250 mg, and 300 mg (F4–F6). The results are illustrated in Fig. 1b, and the f_2 values obtained were 63.96 (200 mg vs. 250 mg), 67.51 (250 mg vs. 300 mg), and 58.26 (300 mg vs. 200 mg).

Figure 1c presents the influence of different NaCl concentrations (20 mg, 35 mg, and 50 mg) on drug release of F7–F9. The drug release rate was observed to increase significantly with the increasing amounts of NaCl. At the test levels, the f_2 values were found to be < 50, i.e., for formulations 20–35 mg (F7 vs. F8), 35–50 mg (F8 vs. F9), and 20–50 mg (F7 vs. F9), the values were 46.05, 47.41, and 34.91, respectively. The influence of drug loading was identified by changing the API content of the tablets (F10–F12). Figure 1d showed the release profiles of

Input parameter	Value	Source
Molecular weight (MW) (g/mol)	435.89	ADMET Predictor™
Log P	1.36	Sengupta et al. ⁴²
pKa	13.6, 1.6	Takács-Novák et al. ⁴³
Solubility (mg/L)		
Aqueous	7	Willmann et al. ⁴⁴
FaSSIF	20	⁴⁴
FeSSIF	80	⁴⁴
Jejunal effective permeability (Peff) (cm/s × 10 ⁻⁴)	3.859	ADMET Predictor™
Unbound percent in human plasma (% F _{up})	5.1	⁴⁴
Human blood to plasma concentration ratio (R _{bp})	0.72	ADMET Predictor™
Cl (L/h)	5.314	PKPlus™
K ₁₂	0.1112	PKPlus™
K ₂₁	0.0714	PKPlus™
V _c (L/kg)	0.5475	PKPlus™

Table 2. Physiological and physicochemical parameters of rivaroxaban for building the PBPK model in GastroPlus™.

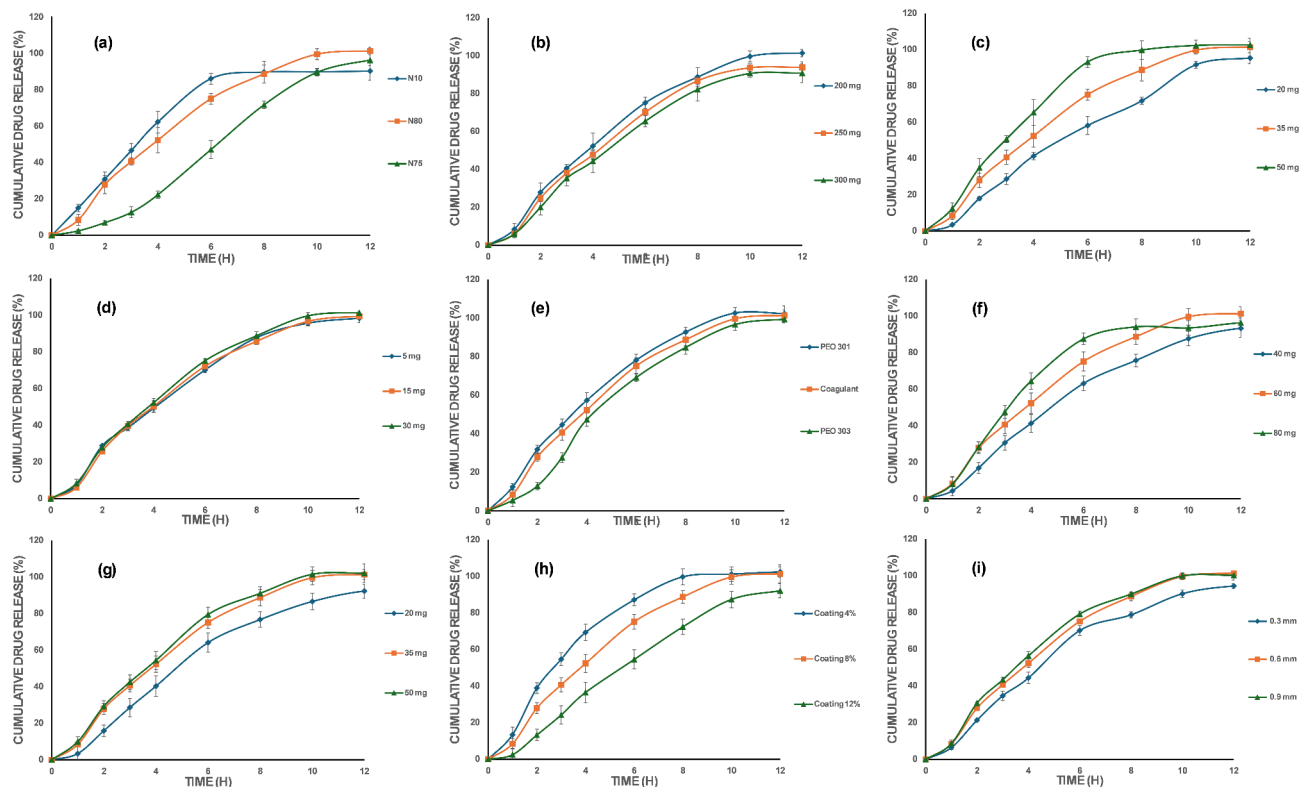


Fig. 1. Screening of the formulation factors for cumulative drug release (%) from rivaroxaban push-pull osmotic tablets.

varying drug amounts of 30, 15, and 5 mg, and the f_2 of each formulation pair was 80.49 (30–15 mg), 76.98 (30–5 mg), and 86.33 (15–5 mg), respectively.

Screening of formulation parameters on the push layer of RVX-PPOP tablets

Three different grades of PEO were tested, i.e., WSR 303 (7000 KDa), WSR Coagulant (5000 KDa), and WSR 301 (4000 KDa) to investigate the influence of PEO molecular weight in the push layer on drug release profiles, f_2 values were calculated to be 62.01 (WSR 301 vs. WSR Coagulant), 51.83 (WSR 301 vs. WSR 303), and 59.07 (WSR 303 vs. WSR Coagulant), respectively indicating that the release profiles of the three formulations (F13–F15) were similar (Fig. 1e). To explore the effect of different amounts of WSR Coagulant (5000 KDa) on the release profile, PEO in the push layer was tested at three levels, i.e., 40 mg, 60 mg, and 80 mg (F16–F18). As shown by Fig. 1f, the drug release rate increased remarkably as the amount of PEO in the push layer increased with the f_2 values smaller than 50 (f_2 : 40–60 mg: 49.72; 60–80 mg: 43.87; 40–80 mg: 34.11). The influence of NaCl amount (F19:20 mg, F20:35 mg, and F21:50 mg) in the push layer on drug release is illustrated by Fig. 1g, and the f_2 values obtained were 49.06 (20 mg vs. 35 mg), 81.32 (35 mg vs. 50 mg), and 45.33 (50 mg vs. 20 mg).

Screening of coating weight gain and orifice diameter on drug release

To investigate their influence on drug release profile, both were tested at three levels, i.e., 4%, 8%, and 12% (F22–F24) and 0.3 mm, 0.6 mm, and 0.9 mm (F25–27), respectively. Figure 1h illustrates that the f_2 values were 4% vs. 8%: 48.64, 8% vs. 12%: 42.31, and 4% vs. 12%: 30.55, respectively. For PPOP, an orifice is created at the drug layer side for the release of drug solution/suspension. Various orifice diameters were generated 0.3 mm, 0.6 mm, and 0.9 mm and evaluated for the change in drug release (F25–F27). As illustrated in Fig. 1i, no significant change was observed as the pore size was changed (f_2 : 0.30 vs. 0.60 mm: 58.32, 0.60 vs. 0.90 mm: 79.58, 0.30 vs. 0.90 mm: 53.40).

Experimental design and micromeritic assessment

Based on the screening data, 20 experimental runs (F1–F20) were obtained from CCD (see Table 3). Before compressing the push and pull layers, the micromeritic properties of all the formulations (F1–F20) powder blends were evaluated and were found to be good to excellent, i.e., angle of repose 22.03°–26.29°, Hausner's ratio 1.09–1.14 and Carr's index 11.34–16.42%, indicating the free-flowing nature of powder blends with good compressibility²⁹.

Compatibility studies by FTIR and DSC analysis

The FTIR spectrum of the pure rivaroxaban (Fig. 2) showed characteristic absorption bands located at 3358 cm^{-1} for tertiary amine C–N (stretching), 3067 cm^{-1} for C–H aryl (stretching), 2914 cm^{-1} for C–H bond, 2867 cm^{-1}

Formulation code	Drug layer					Push layer					Coating weight gain (%)	Orifice diameter (mm)
	Rivaroxaban (mg)	PEO N-80 (mg)	NaCl (mg)	Avicel (mg)	Mg. Stearate (mg)	PEO coagulant (mg)	NaCl (mg)	Avicel (mg)	Mg. Stearate (mg)	Fe ₂ O ₃ (mg)		
F1	30	200	35	32	3	26.36	35	86.64	1.5	0.5	8	0.6
F2	30	200	20	47	3	40	35	73	1.5	0.5	4	0.6
F3	30	200	20	47	3	40	35	73	1.5	0.5	12	0.6
F4	30	200	50	17	3	40	35	73	1.5	0.5	12	0.6
F5	30	200	50	17	3	40	35	73	1.5	0.5	4	0.6
F6	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F7	30	200	60.2	6.8	3	60	35	53	1.5	0.5	8	0.6
F8	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F9	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F10	30	200	9.8	57.2	3	60	35	53	1.5	0.5	8	0.6
F11	30	200	35	32	3	60	35	53	1.5	0.5	14.7	0.6
F12	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F13	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F14	30	200	35	32	3	60	35	53	1.5	0.5	8	0.6
F15	30	200	35	32	3	60	35	53	1.5	0.5	1.3	0.6
F16	30	200	20	47	3	80	35	33	1.5	0.5	4	0.6
F17	30	200	20	47	3	80	35	33	1.5	0.5	12	0.6
F18	30	200	50	17	3	80	35	33	1.5	0.5	12	0.6
F19	30	200	50	17	3	80	35	33	1.5	0.5	4	0.6
F20	30	200	35	32	3	93.6	35	19.4	1.5	0.5	8	0.6

Table 3. Composition of formulation blends obtained from central composite design.

for symmetric -CH_2 (stretching), 1739 cm^{-1} for C=O ester, 1647 cm^{-1} for secondary amine N-H (bending), 1324 cm^{-1} for aromatic tertiary amine C-N (bending), $1300\text{--}1150\text{ cm}^{-1}$ for C-O-C (stretching) for both ethers and esters, 1145 cm^{-1} for secondary amine C-N (stretching), $1100\text{--}1000\text{ cm}^{-1}$ for C-O (stretching), and 769 cm^{-1} for C-Cl (stretching).

Differential scanning calorimetry (DSC) was performed to assess the exothermic or endothermic phase transformations. The thermal behavior of pure rivaroxaban and excipients were determined and compared, and the overlay DSC scans are illustrated in Fig. 3. A sharp endothermic peak at 235°C is indicative of rivaroxaban's melting point, and a little exothermic peak at 334°C presents a carbonization initiation reaction after melting⁴⁹. In contrast, the Avicel PH-102 sample showed a broad endothermic reaction beginning at 43°C with a peak at $\sim 85^\circ\text{C}$. The pure Polyox presented sharp peaks at 72°C and 68°C for WSR-Coagulant and WSR-N-80, respectively.

Physical and chemical evaluation of RVX-PPOP tablets

The mean tablet weight of the trial runs (F1–F20) was $446.12 \pm 3.13\text{ mg}$ to $452.43 \pm 2.01\text{ mg}$, hardness was $7.45 \pm 0.71\text{ kg/cm}^2$ to $10.02 \pm 0.59\text{ kg/cm}^2$, and the maximum percentage friability was $0.61 \pm 0.11\%$. The mean diameter and thickness of the tablets were in the range of $10.00 \pm 0.02\text{ mm}$ to $10.03 \pm 0.03\text{ mm}$ and $5.50 \pm 0.07\text{ mm}$ to $5.53 \pm 0.09\text{ mm}$, respectively (see Table 4). The results of the content uniformity test of each formulation blend ($n = 10$) were $99 \pm 3.45\%$ to $105 \pm 5.34\%$, as illustrated in Table 4, and the chromatogram of the pure API and the optimized formulations are expressed in Fig. S1. The dissolution profiles of all the trial formulations (F1–F20) are given in Fig. 4, and the results demonstrated that formulations having higher coating weight gain control the drug release comparatively better than the formulations with low coating weight gain ($< 85\%$ in 8 h). Meanwhile, the increased osmogen and/or polymer concentrations lead to faster drug release ($\geq 85\%$ in 8 h) and more deviation from the zero-order release kinetics. The evaluation of release kinetics by empirical (zero order, first order, and Higuchi) and non-empirical (Korsmeyer-Peppas and Hixon Crowell) models is illustrated in Table 5.

ANN-assisted prediction of rivaroxaban PPOP tablets

Twenty sets of experimental data ($Y_1\text{--}Y_4$), each with a sample size of 10 runs, were fed into the ANN network for training and testing (70:30) by Random Holdback at Model launch TanH 3–7. The results of activation nodes and generalized coefficient of correlation are illustrated in Fig. 5; Table 6. The prediction profiler obtained on the selected node is represented in Fig. 6.

Numerical and graphical optimization for rivaroxaban PPOP tablets

The polynomial equations express the mathematical relationship among the independent and dependent variables are given in Table 7, and Fig. 7 represents the 3D response surface curves and perturbation plots. The effect of individual input variables on the critical responses is expressed in Table 8. Figure 8 presents the design space, and based on the desirability function, F_{opt} was manufactured and evaluated for critical response factors.

Comparison of the optimized and predicted formulations by ANOVA

The ANOVA (one-way) findings revealed no significant difference between F_{pred} and F_{opt} , as the p -value was 0.9705 ($p \leq 0.05$). The value of $F = 0.0014$ was also in the acceptance region, which is less than the F critical value (4.3512) (see Table 9). This indicates a high level of similarity between the release profiles of optimized and

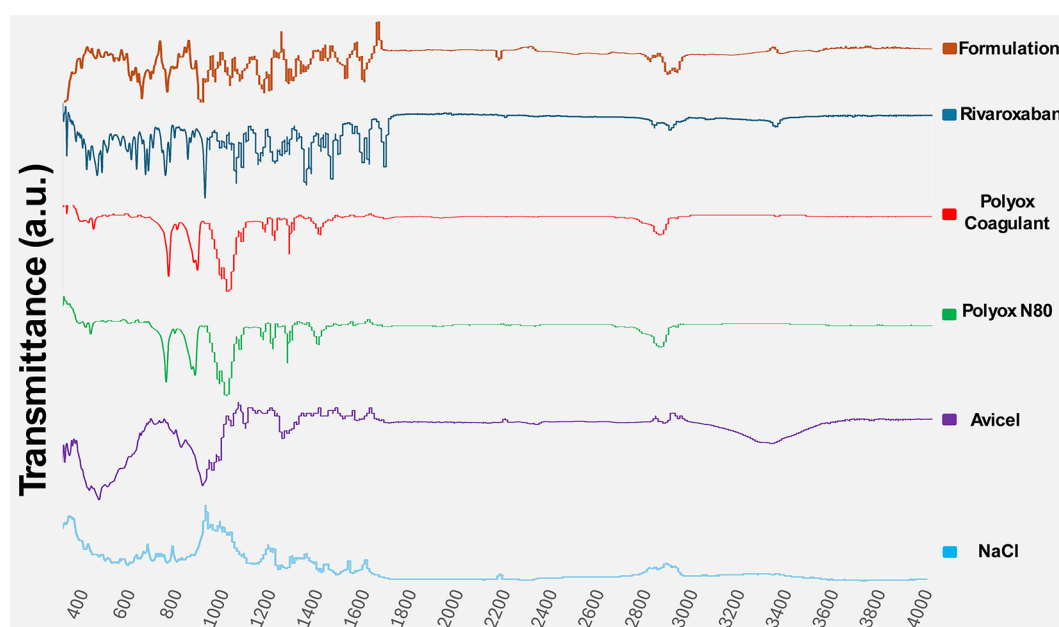


Fig. 2. FTIR spectra of pure API, formulation blend, and formulation components.

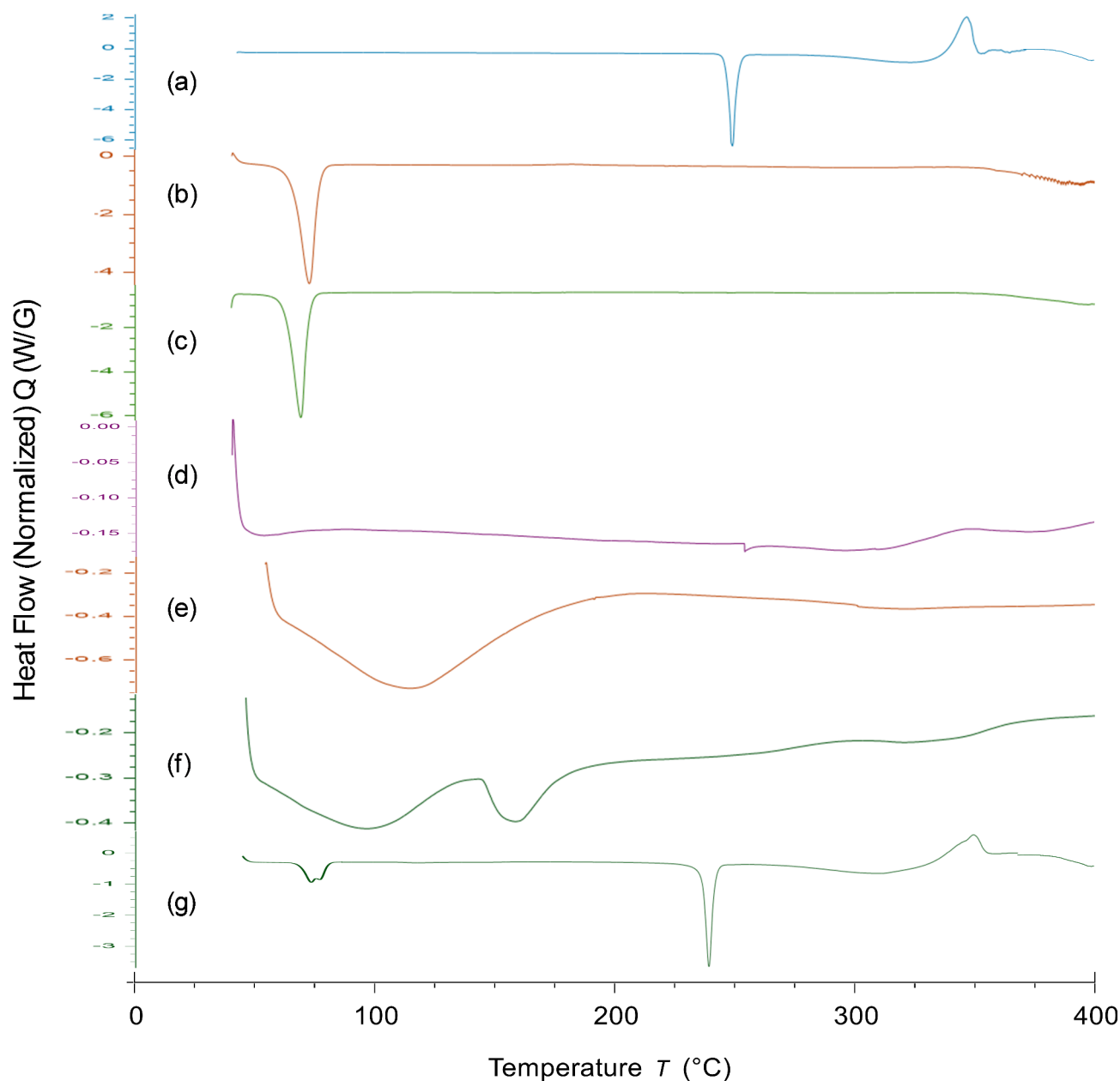


Fig. 3. DSC scans of pure API, formulation blend, and formulation components.

predicted formulations and the difference in the mean dissolution rate of both the formulations was statistically insignificant.

Scanning electron microscopy (SEM) and stability studies

The scanning electron micrograph results of F_{pred} are presented in Fig. S2. The shelf life was also found to be 22.47 months and 17.87 months for F_{pred} and F_{opt} , respectively (Table S1).

In Silico PBPK modeling and simulation of RVX PPOP tablets

The reported pharmacokinetics study of an oral solution of 10 mg RVX was applied for model building; the two-compartmental model was selected with the help of the PKPlus[®] module⁵. Using the 'Human Physiology-Fasted' state, the simulation of the oral solution of 10 mg RVX showed an underestimation of the physiological events of the oral absorption, resulting in poor curve-fitting of the concentration-time profile (See Fig. 9). The PBPK (physiology-based pharmacokinetic) model was developed and verified by predicting the parameters of the RVX 10 mg immediate-release tablets, and the fold error (FE) was found within the acceptable limits, i.e., 1.04–1.20 (Table 10). The in vivo pharmacokinetic profiles of the ANN predicted formulation (F_{pred}) under fed and fasted states were simulated by the developed and tested PBPK model. There was observed a rise in C_{max} under the fed state than in fasting conditions (235.05 vs. 168.1), whereas the T_{max} was reduced (6.66 vs. 8.1). When compared,

Type of tablets	Formulation code	Physical characteristics (n = 20)					Chemical characteristics (n = 20)
		Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg)	Friability (%)	Content uniformity (%)
Uncoated tablets	F1	450.23 ± 2.14	5.52 ± 0.05	10.02 ± 0.01	8.31 ± 2.56	0.44 ± 0.03	101 ± 2.34
	F2–F3	449.34 ± 1.98	5.50 ± 0.07	10.03 ± 0.03	9.12 ± 1.45	0.61 ± 0.11	99 ± 3.45
	F4–F5	446.12 ± 3.13	5.53 ± 0.02	10.02 ± 0.05	7.45 ± 0.71	0.56 ± 0.04	103 ± 1.07
	F–6, F8–F9, F12–F14	451.73 ± 1.87	5.51 ± 0.07	10.03 ± 0.01	7.89 ± 1.24	0.41 ± 0.19	104 ± 1.34
	F7	450.87 ± 3.02	5.53 ± 0.02	10.01 ± 0.04	9.23 ± 0.94	0.39 ± 0.06	103 ± 4.87
	F10	449.88 ± 1.67	5.53 ± 0.09	10.02 ± 0.01	10.01 ± 0.76	0.17 ± 0.06	97 ± 6.34
	F11	450.34 ± 2.22	5.50 ± 0.09	10.01 ± 0.01	8.67 ± 1.34	0.41 ± 0.14	101 ± 3.34
	F15	452.43 ± 2.01	5.52 ± 0.03	10.02 ± 0.01	9.23 ± 2.04	0.38 ± 0.11	105 ± 5.34
	F16–F17	448.29 ± 3.01	5.53 ± 0.09	10.00 ± 0.02	8.34 ± 1.23	0.48 ± 0.02	102 ± 3.39
	F18–F19	450.11 ± 1.87	5.52 ± 0.08	10.03 ± 0.01	10.02 ± 0.59	0.11 ± 0.06	103 ± 1.99
	F20	449.89 ± 2.45	5.53 ± 0.05	10.01 ± 0.05	8.39 ± 0.87	0.43 ± 0.13	101 ± 5.03
Coated tablets	F1	486.24 ± 2.45	5.96 ± 0.04	10.82 ± 0.02	N/A	N/A	105 ± 4.47
	F2	485.28 ± 2.23	5.75 ± 0.06	10.46 ± 0.01			102 ± 2.98
	F3	503.26 ± 2.61	6.19 ± 0.05	11.24 ± 0.03			99 ± 4.26
	F4	499.65 ± 4.18	6.19 ± 0.02	11.22 ± 0.03			101 ± 2.78
	F5	465.31 ± 2.44	5.76 ± 0.04	10.45 ± 0.02			105 ± 3.16
	F6	487.97 ± 2.63	5.95 ± 0.02	10.83 ± 0.04			102 ± 2.76
	F7	486.93 ± 3.41	5.97 ± 0.03	10.81 ± 0.03			103 ± 5.87
	F8	487.97 ± 2.63	5.95 ± 0.02	10.83 ± 0.04			102 ± 2.76
	F9	487.97 ± 2.63	5.95 ± 0.07	10.83 ± 0.02			102 ± 2.76
	F10	485.87 ± 2.56	5.97 ± 0.02	10.82 ± 0.03			97 ± 7.12
	F11	516.63 ± 4.05	6.30 ± 0.04	11.48 ± 0.04			101 ± 2.67
	F12	487.97 ± 2.63	5.95 ± 0.02	10.83 ± 0.04			102 ± 2.76
	F13	487.97 ± 2.63	5.95 ± 0.02	10.83 ± 0.04			102 ± 2.76
	F14	487.97 ± 2.63	5.95 ± 0.02	10.83 ± 0.04			102 ± 2.76
	F15	458.76 ± 1.78	5.59 ± 0.05	10.16 ± 0.02			104 ± 2.67
	F16	469.46 ± 2.35	5.76 ± 0.03	10.42 ± 0.05			103 ± 1.89
	F17	503.42 ± 1.69	6.21 ± 0.04	11.23 ± 0.01			101 ± 3.76
	F18	505.47 ± 3.36	6.19 ± 0.04	11.26 ± 0.06			99 ± 3.79
	F19	467.53 ± 2.27	5.75 ± 0.06	10.43 ± 0.03			103 ± 2.26
	F20	485.69 ± 3.05	5.97 ± 0.01	10.81 ± 0.04			101 ± 4.05

Table 4. Physical and chemical characteristics of the formulation blends.

the AUC_{0-inf} and AUC_{0-t} under the fed condition were greater than the fasted state, i.e., 3990 vs. 3280.5 and 3648.1 vs. 2980.6, respectively (See Table 10).

Discussion

Screening of formulation parameters on drug layer of RVX-PPOP tablets

The grade and concentrations of polyethylene oxide (PEO), sodium chloride, and RVX were screened for the percentage of drug release by comparing the in vitro drug release profiles obtained up to 12 h. Different grades and concentrations of PEO influence the drug release due to its variable swelling characteristics. The right strength of the osmotic agent (sodium chloride) used will lead to the formation of the suspension in situ due to water imbibition associated with the generation of osmotic pressure. The volumetric expansion of the push layer aids the efflux of this drug suspension out of the delivery orifice present over the drug layer. For developing PPOP, different strengths of RVX were also tested to ascertain that the cumulative percentage drug release from PPOP is independent of drug dose⁵⁰.

PEO (N-80) was found to be a suitable swelling agent in the drug layer because of complete drug release without burst effect; this may be attributed to excessive swelling of the polymer in the later stages. Meanwhile, N-10 exhibited relatively quicker and incomplete release, and N-750 showed comparatively greater lag time. PEOs with low MW (100–600 kDa) are usually utilized in the drug layers to acquire the zero-order release profiles⁵⁰, as they are hydrated fast in the initial 3–4 h, forming a flowable suspension^{51,52}. However, the percentage of drug release was found to be complete with 200 mg N-80 as compared to 250 mg and 300 mg, which may be associated with the increases in viscosity of drug suspension⁵³.

This variation of osmotic agent demonstrated that NaCl in the drug layer was an essential factor, as it could influence the drug release significantly; therefore, in the present work, NaCl was further tested by CCD in the range of 20–50 mg in the drug layer⁵⁴. The change in API amount in the drug layer indicated that the percentage of drug release is independent of the drug amount tested. Based on the current observation, it can be stipulated

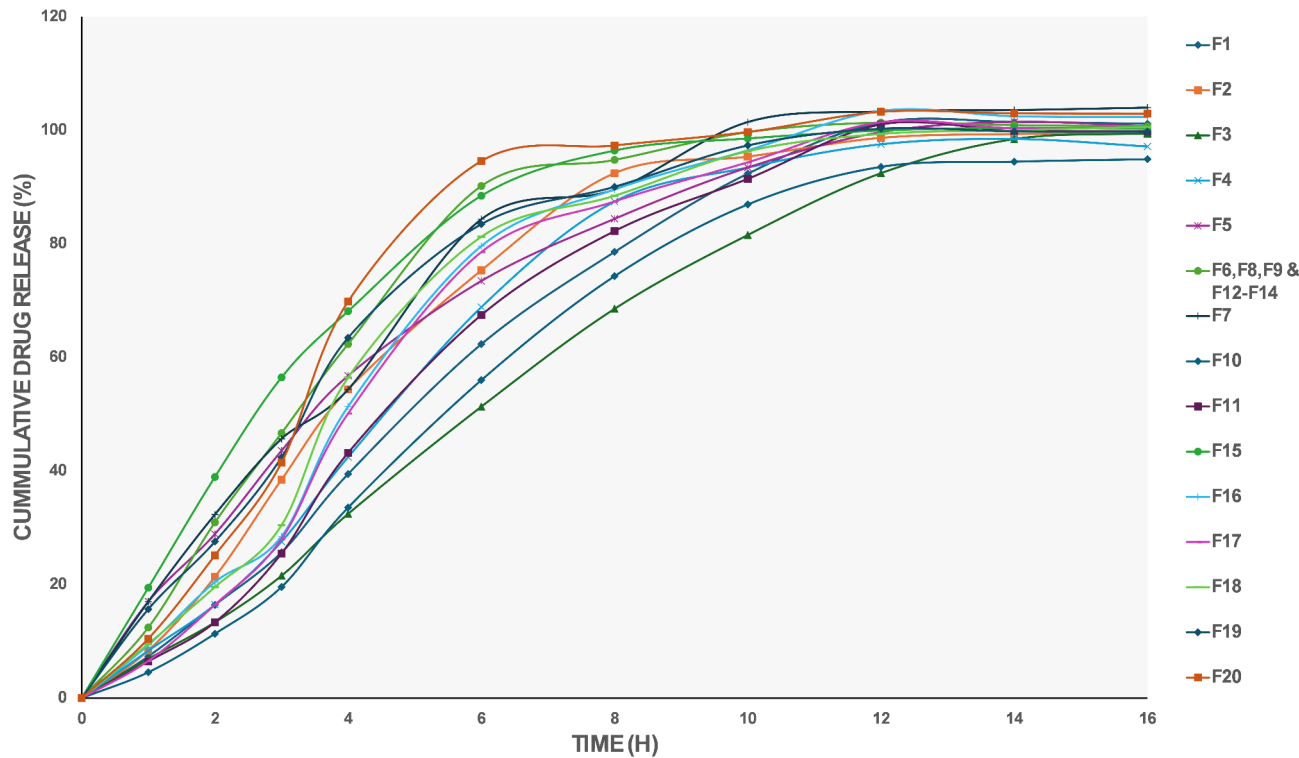


Fig. 4. Dissolution release plots (%) of formulations (F1–F20) designed by central composite design ($n = 6$).

Formulations	Zero Order		First Order		Higuchi		Korsmeyer-Peppas			Hixon Crowell		Weibull		
	k_0	Rsqr	k^{-1}	Rsqr	kH	Rsqr	kKP	n	Rsqr	kHC	Rsqr	α	β	Rsqr
F1	9.135	0.994	0.141	0.933	25.471	0.866	10.854	0.921	0.988	0.046	0.962	65.623	2.123	0.998
F2	9.926	0.988	0.196	0.935	28.326	0.909	18.284	0.719	0.957	0.058	0.978	12.509	1.621	0.999
F3	8.045	0.995	0.112	0.942	22.294	0.848	8.263	0.988	0.993	0.038	0.966	54.143	1.899	0.999
F4	9.387	0.993	0.160	0.908	26.377	0.872	13.189	0.844	0.965	0.050	0.962	45.537	2.074	0.999
F5	9.835	0.966	0.205	0.990	28.392	0.966	22.002	0.628	0.986	0.059	0.999	7.951	1.306	0.998
F6	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F7	10.460	0.964	0.227	0.969	30.192	0.954	23.274	0.631	0.975	0.066	0.988	15.678	1.711	0.991
F8	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F9	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F10	8.401	0.986	0.119	0.901	23.210	0.827	8.347	1.003	0.979	0.040	0.950	34.390	1.832	1.000
F11	9.281	0.984	0.150	0.907	25.926	0.860	11.634	0.897	0.973	0.048	0.957	24.285	1.810	0.997
F12	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F13	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F14	10.629	0.959	0.248	0.947	30.798	0.931	24.782	0.610	0.946	0.071	0.983	15.063	1.842	0.998
F15	10.764	0.939	0.288	0.982	31.645	0.957	31.084	0.509	0.957	0.080	0.998	5.735	1.367	0.999
F16	10.001	0.976	0.185	0.906	28.297	0.886	15.926	0.787	0.957	0.056	0.959	45.414	2.192	0.995
F17	9.773	0.971	0.176	0.895	27.562	0.870	14.749	0.811	0.951	0.054	0.954	18.160	1.816	0.996
F18	9.935	0.964	0.193	0.909	28.273	0.889	17.479	0.741	0.944	0.057	0.962	19.748	1.867	0.993
F19	10.291	0.957	0.229	0.959	29.761	0.941	23.432	0.621	0.958	0.066	0.988	11.053	1.595	0.996
F20	10.818	0.943	0.252	0.902	31.242	0.895	23.872	0.636	0.917	0.072	0.957	287.541	3.316	0.997

Table 5. The release rate and coefficient of correlation of rivaroxaban push-pull osmotic formulations calculated using the model-dependent kinetics.

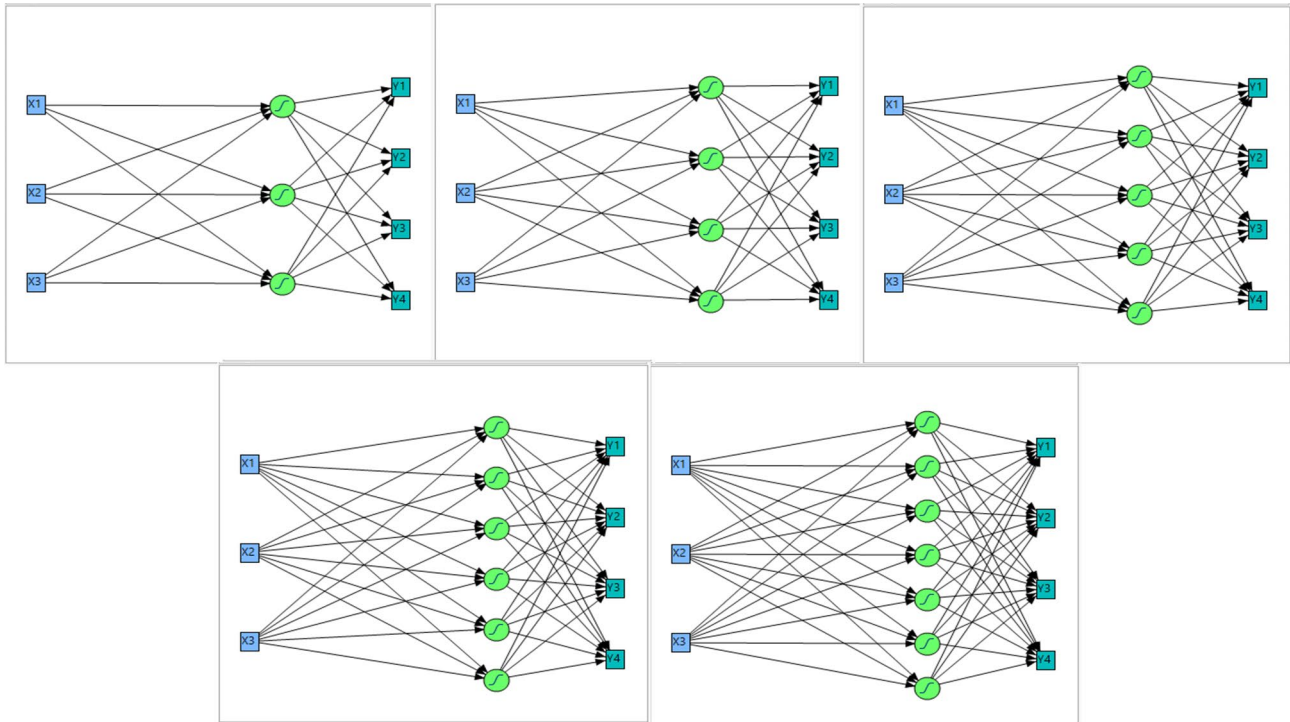


Fig. 5. MLP (Multilayer perceptron) architecture for a feed forward back propagation ANN model where $X_1 - X_3$ are the inputs and $Y_1 - Y_4$ represents output factors at different nodes.

Correlation coefficient values of critical output parameters at different nodes										
Node	Generalized co- rrelation		Y1		Y2		Y3		Y4	
	Training	Testing	Training	Testing	Training	Testing	Training	Testing	Training	Testing
	r^2 , SSE									
3	0.9999	0.9996	0.784, 194.612	0.804, 59.17	0.894, 183.33	0.863, 170.211	0.898, 17.16	0.862, 8.857	0.953, 0.004	0.891, 0.003
4	0.9972	0.9995	0.845, 139.22	0.924, 22.808	0.775, 391.58	0.714, 356.87	0.703, 50.05	0.343, 42.162	0.729, 0.022	0.963, 0.001
5 ^a	1	1	0.905, 84.904	0.675, 98.121	0.985, 24.491	0.996, 4.384	0.886, 19.215	0.893, 6.90	0.862, 0.011	0.700, 0.007
6	0.9881	0.9991	0.726, 246.16	0.393, 182.89	0.788, 369.226	0.943, 70.250	0.448, 93.13	0.950, 3.15	0.625, 0.031	0.449, 0.015
7	0.9997	0.9997	0.870, 116.41	0.940, 18.005	0.888, 194.901	0.847, 190.69	0.824, 29.674	0.197, 0.01	0.874, 0.01	0.955, 0.001

Table 6. Selection of nodes for ANN model. Significant values are in [bold]. ^aNode 5 has the highest overall or generalized value of r^2 and minimum sum of square error (SSE).

that the drug is delivered from the orifice as a comparatively high viscous hydrogel suspension; however, the robustness in PPOP formulations was observed for the drugs less than or equal to 30%⁵⁵.

Screening of formulation parameters on the push layer of RVX-PPOP tablets

The primary contributor to the drug release in PPOP tablets is the polymer present in the push layer and its water uptake properties. As previously reported, the swelling ratio of polyethylene oxide is directly related to the molecular weight and number of units of the polymer⁵². Therefore, as the molecular weight of the PEO was increased, the percentage drug release was observed to be increased due to greater volume expansion after more water uptake, resulting in the complete pushing of drug suspension through the orifice. In the current work, WSR Coagulant (5000 KDa) was selected for further studies due to complete drug release, whereas WSR 303 and WSR 301 showed greater lag time and incomplete release, respectively. Coagulant (5000 KDa), by its high molecular weight in the push layer, acts as a promising swelling agent and controls the release of the active moiety either by the mechanism of swelling or by swelling/erosion⁵¹. It was also observed that when the amount of PEO in the push layer was increased (e.g., 80 mg), the PEO suspension in the drug layer remained undischarged from the orifice in due time, and the coating membrane was also deformed, resulting in an erratic release pattern at the later phase of drug release. Based on the above observation, the amount of Coagulant (5000 KDa) tested by CCD for the optimization process was 40–80 mg⁵⁶.

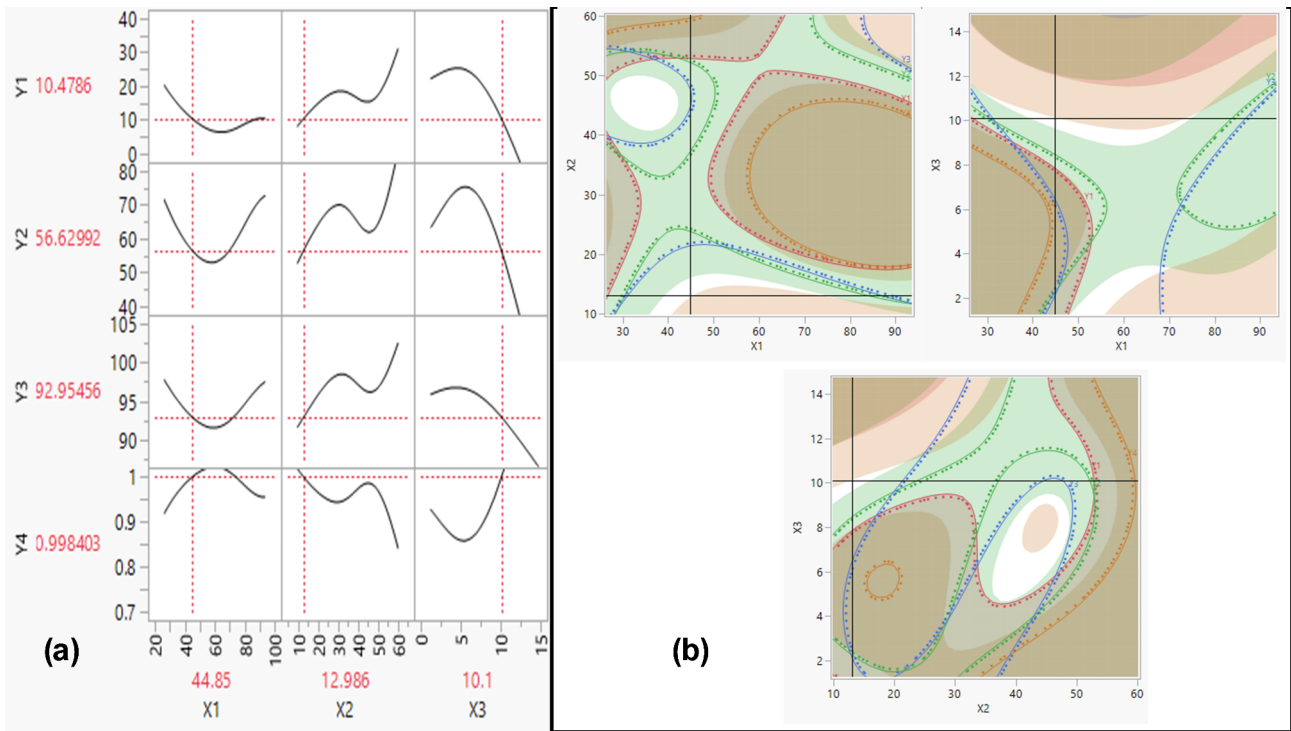


Fig. 6. Profilers based on the prediction developed by the MLP model: (a) prediction profiler for the desired response and (b) contour profiler of different input variables.

Predicted input variables	Predicted output variables	Equations in terms of coded factors
X1 44.85	Y1 (DR @ 1 h: <20%) *	$Y1 = 30.99 + 1.43 A + 4.18 B - 5.59 C - 0.165 AB + 1.16 AC - 0.9425 BC - 4.02 A^2 - 3.65 B^2 - 2.12 C^2$
X2 12.986	Y2 (DR @ 6 h: 40 – 60%)	$Y2 = 90.18 + 8.14 A + 5.34 B - 5.14 C - 0.7637 AB + 2.79 AC + 1.9 BC - 4.21 A + -7.14 B^2 - 4.38 C^2$
X3 9.057	Y3 (DR @ 12 h: >85%)	$Y3 = 99.67 + 2.18 A + 1.7 B - 0.6935 C$
	Y4 (RSQ _{Zero} : 0.99–1.00)	$Y4 = 0.8178 - 0.0301 A - 0.0278 B + 0.0487 C - 0.0062 AB - 0.0132 AC + 0.0058 BC + 0.0338 A^2 + 0.0423 B^2 + 0.0119 C^2$

Table 7. Predicted output variables and model equations using graphical & numerical approach. *Targeted constraints for each response.

An increase in the amount of NaCl causes an increase in the release rate of Rivaroxaban. The quick hydration and swelling of the push layer lead to the greater pushing force generated in the coating membrane and, consequently, rapid drug release. Lin S.Y. et al. also reported that an increase in the osmotic agent amount enhances the dissolution rate and faster drug release from the core tablet⁵⁷. In the current study, no difference was observed in the release profiles of F20 and F21, so the minimum amount of NaCl required to achieve the appropriate osmotic pressure was selected as 35 mg for further studies.

Screening of coating weight gain and orifice diameter on drug release

The tablet coating weight gain and orifice diameter significantly affect the drug release rate, which depends on the fashion of the water imbibition through the coating membrane. The results indicated that an increase in the coating thickness caused an inadequate driving force for water uptake, resulting in a poor drug release rate; contrarily, a thinner coating membrane produced less resistance to water influx. However, too thin a coating membrane results in a very fragile mechanical barrier, which could be cracked if the internal pressure exceeds the tensile strength of the layer, leading to abrupt and erratic drug release⁵⁸. Therefore, in the current work, coating weight gain in the range of 4–12% was further investigated by CCD at five levels.

No significant changes in drug release were observed as the pore size was altered but in the case of 0.3 mm, there was observed tablets deformation because of the mechanical pressure generated due to the expansion of polymers inside. For further studies, 0.6 mm was selected as a moderate orifice size to reduce the contribution to the rate of drug diffusion through the orifice and to minimize the osmotic pressure generated inside^{59,60}.

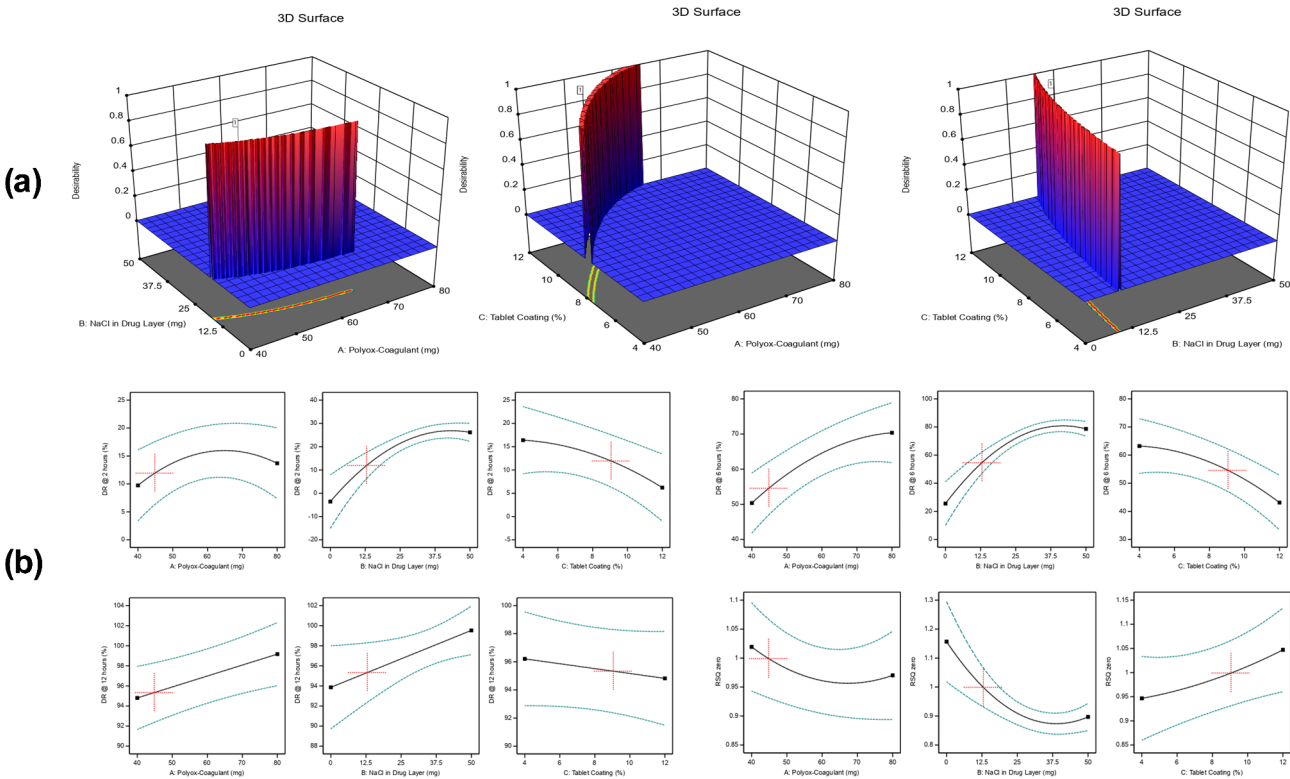


Fig. 7. Design space created by numerical optimization: (a) response surface desirability plot and (b) perturbation effect plot.

Response	Model	F-Value	P-value for model	P-value for variables		
				X1	X2	X3
Y1	Quadratic	11.73	0.0003	0.1373	0.0008	<0.0001
Y2	Quadratic	16.2	<0.0001	<0.0001	0.0012	0.0015
Y3	Linear	4.83	0.014	0.0102	0.0374	0.3685
Y4	Quadratic	6.91	0.0028	0.0177	0.026	0.001

Table 8. Analysis of variance (ANOVA) for fitness of the model.

Experimental design

The application of CCD produced 20 experimental formulations (F1–F20), including six central points. Keeping PEO Coagulant (X_1 ; 40–80 mg), NaCl amount in the drug layer (X_2 ; 20–50 mg) and percentage coating weight gain (X_3 ; 8–12%), as independent variables, their impact on percentage drug release (Y_1 ; %DR at 2 h, Y_2 ; %DR at 6 h and Y_3 ; %DR at 12 h) and zero-order coefficient of regression (Y_4 ; RSQ_{Zero}) was critically evaluated. Xin Tang (2013) designed and evaluated gliclazide push-pull osmotic tablets and used PEO-N-80 and PEO WSR-303 in the drug and push layers, respectively⁶¹. Similarly, Xiaohong Liu also developed Nimodipine PPOP tablets (2014) using solid dispersion techniques and different molecular weight PEO to control the drug release⁶². Another study by Yuenan Li in 2019 suggests that the amount and type of PEO are critical for developing actarist double-layered osmotic pump tablets⁶³.

Compatibility studies by FTIR and DSC analysis

The characteristic fingerprints of the pure rivaroxaban, polymers (Polyox Coagulant and Polyox N-80), Avicel PH-102, and sodium chloride spectra remained unaffected in the formulation blend, indicating the absence of any interaction among them⁶⁴. The absence of any extra peak in the DSC spectrum shows that the drug is homogeneously distributed in the amorphous state^{65,66}.

Physical and chemical evaluation of RVX-PPOP tablets

The mechanical strength (percentage friability and hardness) of the tablets of all the trial batches was found satisfactory in terms of withstanding the mechanical shock during the coating process. Uniformity of thickness and diameter is essential to create a smooth coating layer on the tablet surface, which is a prerequisite to cause consistent water imbibition. All the batches met the official requirements of weight variation and chemical

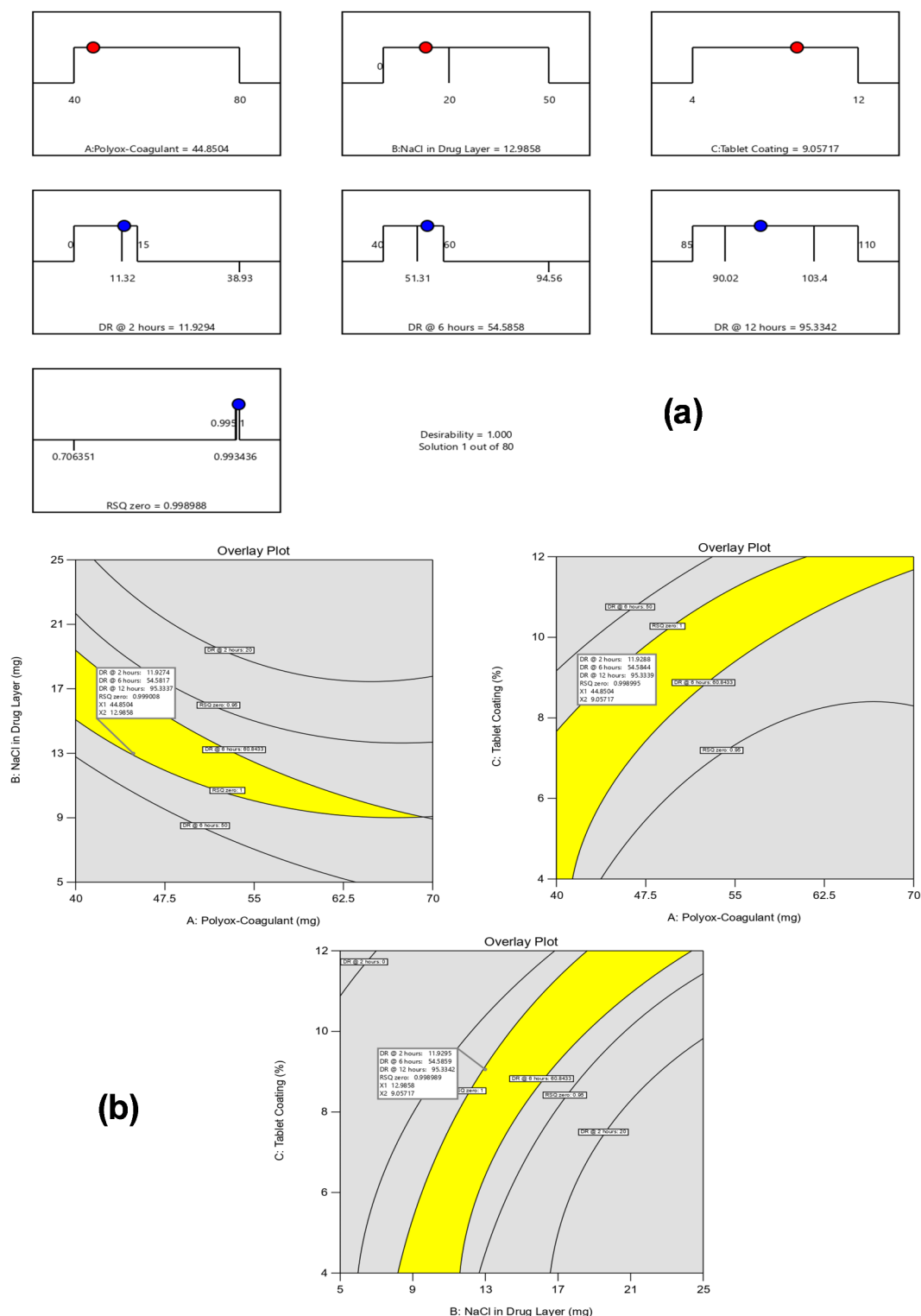


Fig. 8. Recommended design space for the selection of optimized rivaroxaban PPOP tablets: (a) Ramp plots by numerical optimization and (b) Overlay plots by graphical optimization.

assay^{29,34}. The coefficient of correlation (r^2) was estimated using DD Solver, and zero-order (r^2 : 0.943–0.995) and Hixon Crowell (r^2 : 0.991–0.999) models were found to be the best-fitted release kinetic models. Our results demonstrated that most of the formulations followed a constant pattern of drug release as a zero-order profile due to the optimum balance between the osmotic agent and the swelling polymer^{67,68}. Similarly, higher values of the coefficient of correlation for the Hixon Crowell model are indicative of the decrease in the total volume of tablets' surfaces due to the continuous removal of core material from the inside. Based on the dissolution results,

Groups	Count	Sum	Average	Variance			
F _{pred} (ANN)	11	561.34	51.03091	1463.004			
F _{opt} (CCD)	11	554.57	50.41545	1507.324			
Source of variation	SS	df	MS	F	P-value	F crit ^a	
Between Groups	2.083314	1	2.083314	0.001403	0.970495	4.351244	
Within Groups	29703.27	20	1485.164				
Total	29705.36	21					

Table 9. ANOVA for the predicted formulations by F_{pred} (ANN) and F_{opt} (CCD). Note: There is no significant difference between both formulations at p > 0.05. ^a The value of F (0.0014) lies in the acceptance region that is less than the F critical value (4.3512).

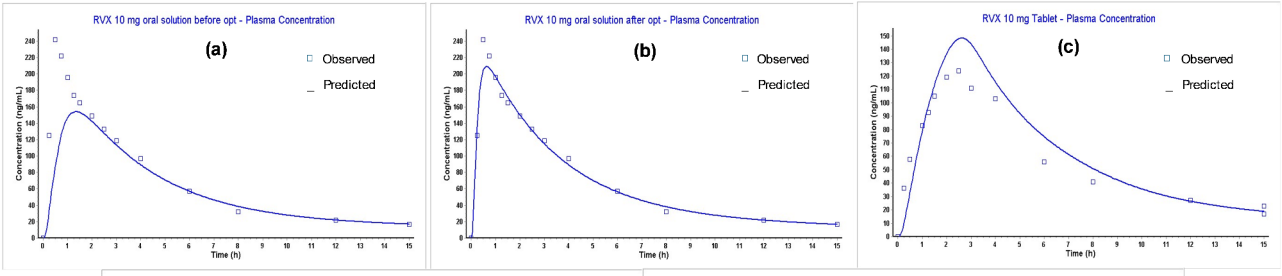


Fig. 9. Observed and simulated rivaroxaban plasma concentration-time profiles of (a) 10 mg oral solution before optimization, (b) 10 mg oral solution after optimization, (c) 10 mg oral IR tablet, (d) 30 mg PPOP tablet under fasted conditions, and (e) 30 mg PPOP tablet under fed conditions.

	Oral solution (10 mg) before optimization			Oral solution (10 mg) after optimization		
Pharmacokinetic parameters	Observed	Predicted	Fold error	Observed	Predicted	Fold error
C _{max} (ng/mL)	242	154.11	0.64	242	209.08	0.86
T _{max} (h)	0.5	1.35	2.70	0.5	0.65	1.30
AUC _{0–inf} (ng·h/mL)	1187.7	1128.5	0.95	1187.7	1191.8	1.00
AUC _{0–t} (ng·h/mL)	989.88	867.25	0.88	989.88	972.23	0.98
	Oral tablet (10 mg)					
Pharmacokinetic parameters	Observed	Predicted	Fold error	Oral tablet (30 mg) Fasted		Oral tablet (30 mg) Fed
C _{max} (ng/mL)	124	148.33	1.20	168.1		235.05
T _{max} (h)	2.5	2.6	1.04	8.1		6.66
AUC _{0–inf} (ng·h/mL)	1043.2	1145.9	1.10	3280.5		3990
AUC _{0–t} (ng·h/mL)	843.25	943.57	1.12	2980.6		3648.1

Table 10. Simulated and observed pharmacokinetic parameters of rivaroxaban PPOP tablets.

three dissolution points, i.e., %DR at 2, 6, and 12 h (Y_1 – Y_3) and zero-order release coefficient, i.e., RSQ_{Zero} (Y_4), were set as output variables for further prediction and optimization using ANN and QbD tools.

ANN-assisted prediction of Rivaroxaban PPOP tablets

An ANN-based multivariate approach was applied after the supervised training of the model for the prediction of in vitro release from Rivaroxaban PPOP. The best activation node obtained was 5, showing the maximum value of the generalized coefficient of correlation for training and testing ($r^2=1$) with the least value of SSE (sum of square errors) for all the variables (training; $Y_1=84.904$, $Y_2=24.49$, $Y_3=19.21$ and $Y_4=0.011$) (testing; $Y_1=98.12$, $Y_2=4.38$, $Y_3=6.89$ and $Y_4=0.007$). For the subsequent higher nodes over training were observed, showing a fall in the values of coefficient of correlation (neural node 6; training $r^2=0.9881$, testing $r^2=0.991$) (neural node 7; training $r^2=0.9997$, testing $r^2=0.9997$) and comparatively higher SSE. Patel et al. incorporated ANN in developing controlled porosity osmotic tablets for the pH-dependent soluble drug Isradipine and optimized neural node five based on the highest r^2 and lowest root mean square values⁶⁹. The data training was stopped further to avoid overfitting, and a prediction profiler was generated at node 5 to get the optimum levels of PEO, sodium chloride, and percentage weight gain after coating (F_{pred}). Ibric et al. utilized GRNN contour plots to observe the effect of Eudragit percentage and tablet hardness on the cumulative drug release

of extended-release aspirin tablets⁷⁰. Similarly, Simões et al. explained the importance of a prediction profiler in simultaneously observing the effects of input variables on the pharmaceutical tablet manufacturing of a class IV drug⁷¹.

Numerical and graphical optimization for Rivaroxaban PPOP tablets

In the current work of numerical and graphical optimization, a well-defined technique was applied to get the finest levels of independent variables (X_1 – X_3) to achieve the targeted critical responses (Y_1 – Y_4). These quantities of PEO (X_1), sodium chloride (X_2), and coating weight (X_3) were also computed by the polynomial equations of each response factor to get the targeted constraints. According to the fit summary (ANOVA), the best model fitted to Y_1 (%DR @1 hr.), Y_2 (%DR @ 6 h.), and Y_4 (RSQ_{Zero}) responses was a quadratic model, whereas drug release at 12 h (Y_3) followed a linear model ($p < 0.05$). The effect of PEO (X_1) was insignificant on drug release at 2 h (Y_1), but the drug release was observed to be significantly increased with the increasing concentration of PEO. It was observed that sodium chloride (X_2) significantly increased the drug release at 2, 6, and 12 h (Y_1 – Y_3), but RSQ_{Zero} decreased considerably with the increasing concentration of osmogen. Coating weight gain (X_3) reduced the drug release at initial hours (2 and 6 h) considerably but did not affect cumulative drug release at 12 h; however, RSQ_{Zero} improved with the rise in coating weight gain. Shah HP and Prajapati ST also applied numerical and graphical optimization to develop gastroretentive floating osmotic capsules of clopidogrel bisulfate⁷².

Comparison of the optimized and predicted formulations by ANOVA

To cross-validate the prediction of the developed ANN model, analysis of variance was applied, and the critical response variables (Y_1 – Y_4) were compared obtained from the predicted formulation (F_{pred}) by the developed ANN model and the optimized formulations (F_{opt}) by numerical and graphical optimization. Yuksel et al.⁷³ discussed ANOVA-based methods' applicability and usefulness in comparing in vitro dissolution profiles of film-coated naproxen tablets.

Scanning electron microscopy (SEM) and stability studies

The F_{pred} scanning electron micrographs of the coated tablets before dissolution revealed the existence of an even and uncomplicated layer of Opadry® CA coating devoid of any surface pores or cracks. As reported in the literature by Verma et al., the increasing concentration (0–55%) of pore former (polyvinyl pyrrolidone) increases the percentage porosity due to dissolution medium imbibition, leading to the expected effect on the percentage drug release. In contrast, the development of numerous micropores was observed on the surface of the tablets after dissolution (and overnight drying)⁷⁴. Following the ICH guidelines (International Council for Harmonization, 2003) for the accelerated conditions, F_{pred} and F_{opt} formulations were placed at 40 ± 5 °C and 75 ± 5 % RH. Various quality tests, including assay, dissolution, and disintegration tests, were performed during the study period of 0, 3, and 6 months. Both formulations expressed good quality characteristics and were found stable. Many reported studies have also demonstrated that osmotic drug delivery systems, when subjected to stability evaluation, retained their physicochemical characteristics and remained stable for an extended period with suitable shelf lives^{65,75,76}.

In Silico PBPK modeling and simulation of RVX PPOP tablets

The prediction of the pharmacokinetic profile and parameters of F_{pred} was carried out using the ACAT® model. During the model development stage, the simulation of the oral solution of 10 mg RVX showed a decrease in plasma concentration. The underprediction may be due to the regional pH variation, influx transporters, efflux proteins, and differences in surface-to-volume ratio throughout the gastrointestinal tract. In the current work, the underpredicted absorption phase of the concentration-time profile was adjusted by scaling the regional effective permeability (P_{eff}) using the ASF (absorption scaling factor) multiplier model Opt logD Model SA/V 6.1. It is evident from Fig. 9 that the bioavailability curves of F_{pred} under fed and fasted states are dissimilar, which may be because of faster dissolution and subsequent absorption of RVX under fed conditions. It has been previously reported that the presence of bile salts that are released after a meal is supportive of increasing the RVX solubility and its subsequent absorption from the duodenum and proximal segment of jejunum, resulting in a significant rise in oral bioavailability up to 27–35%⁷⁷. The current predictive results suggest that the fed state bioavailability was improved (up to 82%) with the administration of RVX PPOP vis-à-vis the IR tablet due to the temporal release of the drug from the system, which may allow continuous absorption from the gut wall and avoid immediate saturation of the lumen. Alam N et al. also reported the enhanced bioavailability of trimetazidine osmotic tablets compared to the marketed formulation due to enhanced gastro retention and absorption⁷⁸.

Conclusion

In the current study, a neural computing framework based on an ANN model was effectively used to speculate the critical response variables for a bilayer push-pull osmotic tablet formulation of a sparingly soluble drug, rivaroxaban. The formulation parameters were initially screened to assess the critical factors influencing the drug release. The predicted formulation of the ANN tool following model training was examined and cross-validated using the proven multivariate CCD technique. The optimal osmotic pump tablet delivered the drug in a zero-order pattern for up to 12 h, demonstrating their usefulness for developing controlled-release tablet formulations. The PBPK modeling of the predicted formulation showed improved oral bioavailability in the fasting state compared to the available immediate-release marketed formulation. Thus, based on the in-silico pharmacokinetic model, it is possible to formulate controlled-release osmotic tablets for drugs with distinctive inter-personal pharmacokinetic variability. The proposed approach considers information on the formulation

of an ODDS and the ability to evaluate compositional quality and key parameters to guide formulation research. This is a bivariate model of ANNs and QbD that can be applied in the future to many areas of other dosage forms and pharmaceutical research. Implementation of these predictive models could effectively reduce the timeline and material use of drug development and proactively promote the development of robust drug products.

Data availability

The results from the present investigation are available from the corresponding author upon reasonable request.

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M.T.S has done major investigation, analysis, software, writing draft preparation. M.H.S involves in conceptualization, methodology, supervision, software, writing- reviewing and editing, R.I.Y helped in methodology, software, validation, writing- reviewing and editing, F.S has done some analysis and method validation.

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