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Research Article

ENHANCEMENT OF SOLUBILITY OF RIVAROXABAN AND FORMULATION OF ITS FAST DISINTEGRATING TABLETS: USING DESIGN OF EXPERIMENTS

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ABSTRACT

The main goal of the experiment was to increase rivaroxaban's solubility and rate of dissolution by preparing the solid dispersions with Poloxamer 188. Additionally, the chosen Poloxamer 188 solid dispersions are intended to create fast disintegrating tablets employing a predetermined concentration of povidone (PVP K30), sodium starch glycol, and PEG 4000 as hydrophilic polymer. At 37 ± 0.5 ºC, the phase solubility behaviour of rivaroxaban was investigated in the presence of varying concentrations of poloxamer 188, PEG 4000, and PVP K30. Negative Gibbs free energy values signify the solubilization of rivaroxaban is spontaneous. The drug Poloxamer 188 solid dispersions are formed into fast disintegrating tablets using the direct compression process. Design, development, and data interpretation were made employing the response surface modelling technique (23 complete factorial design). Utilizing Design Expert 11 (Stat-Ease Inc., USA) for analysis, the reactions to the design were examined. Based on software analysis and an overall attractiveness factor, the optimal formulation was chosen. The improved formulation had a 30-40 second disintegration time, a friability of 0.21 percent, and a release of more than 85 % in 30 minutes. Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), were used to characterize the physicochemical properties of the solid dispersions and the tablet formulation.

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INTRODUCTION

The key physicochemical factors limiting a novel drug molecule's bioavailability are its water solubility and penetration across biological membranes. There are several ways to improve the solubility of drugs that do not dissolve well in water. These methods include chemical modifications like creating pro-drugs or salt derivatives, physical modifications like breaking down the drug into smaller particles or combining it with porous materials, changing the composition of the solvent by adjusting the pH or adding surfactants, and using carrier systems like polymers, cyclodextrins, micelles, and liposomes. Utilizing hydrophilic polymer solid dispersions is a straightforward and practical solubilizing method. An effective method to increase solubility is solid dispersions with poloxamer, which increases the bioavailability and dissolving rate of biopharmaceutical categorization system. Pharmaceutical solubilizing excipients like poloxamer can temporarily enhance physicochemical characteristics while providing beneficial therapeutic and formulation features. Under specific conditions, poloxamer can improve oral dosage availability, drug stability, and influence permeability through biological membranes.

In solution, poloxamer forms solid dispersions that aids in the solubilization of hydrophobic drug. Drug-poloxamer delivery methods are responsible for advancements in an ever-growing range of therapies, each with its own special difficulties. Considering the Noyes-Whiney connection, poloxamer solid dispersions is frequently utilized to increase the oral bioavailability of poorly soluble drugs [1-2].

Rivaroxaban is an oral anticoagulant (blood thinner) medication. The compound (S)-5-chloro-n- [2- oxo-3[3-oxomorpholin-4-yl] phenyl] oxazolidin-5-yl] rivaroxaban is referred to by the IUPAC as methyl thiophene-2-carboxamide. It is marketed as Xarelto, which is a brand name for a medication.[3] Additionally, thrombosis of the deep veins (DVT), which may lead to pulmonary blood clots (pulmonary embolism) is treated and prevented with rivaroxaban. As an anticoagulant, rivaroxaban works by inhibiting the formation of blood clots [4]. It was created by Bayer and distributed by Janssen Pharmaceuticals in the US. Rivaroxaban was patented in the US in 2007 and got FDA clearance for medical use in 2011. The patent on rivaroxaban expires in 2024.

It is the first active direct factor Xa inhibitor to be taken orally. The bioavailability of rivaroxaban is dose dependent. Meals have no impact on the bioavailability of the 10 mg dosage, which is between 80 and 100 %. Even though exposure is enhanced when

taken with meals, the bioavailability of the 20 mg dosage when given while fasting is just 66 %. It is advised to take the 15 mg and 20 mg doses with your evening meal. Depending on the location in the GIT where the medication is released, rivaroxaban is absorbed slowly. In this experiment, a production run of rivaroxaban immediate-release tablets was attempted. Rivaroxaban is available in marketed formulations; however, they are quite expensive and unaffordable for those on limited budgets. As a result, formulations that are more affordable than those on the market are produced. The purpose of this study is to improve rivaroxaban's solubility and tablet formulation utilizing the direct compression technique. The objective is to speed up the process by which the substance breaks down in the small intestine. Direct compression is a practical technique. Its efficacy, simplicity, and cost-effectiveness are being studied. The process is much faster. [1-8].

MATERIALS AND METHODS

Materials

Rivaroxaban was received from M/s Aurobindo Pharma Limited, Hyderabad, India, as a gift sample. Excipients from Aurobindo Pharma Limited in Hyderabad, India, include Poloxamer 188. Colorcon Asia Pvt. Ltd., Verna, Goa, India, provided PEG 4000. We purchased Povidone K30 from Balaji Amines Limited in Hyderabad, India. Talc, magnesium stearate, and sodium starch glycolate were provided by Research-Lab Pellets Pharma Limited in Hyderabad, India. Other chemicals and solvents employed in the investigation were of the analytical grade.

Phase solubility studies

By adding extra rivaroxaban to various concentrations of poloxamer 188, PEG 4000, and PVP K30 in water ranging from 1 to 3 % in screw-capped glass vials, Higuchi and Connors' technique was used to determine rivaroxaban's solubility. A specific volume was taken out and filtered via a 0.45 micrometre polyvinylidene difluoride (PVDF) membrane (Sterlitech corporation, USA) after two days of mixing in a water bath shaker (Remi Pvt Ltd, Mumbai). Using Shimadzu 1800 UV-Visible spectrophotometer, samples were examined at 270 nm with the appropriate dilution. Without using hydrophilic carriers, the drug's saturation solubility in distilled water was also measured. Rivaroxaban's Gibbs free energy values for varying carrier concentrations in water were calculated from equation 1

$\Delta G_{tr}^{0} = -2.303\ RT \log (S_o/S_S)$ - -Equation 1

Here, (S_o/S_S) is the ratio of molar solubility of drug in aqueous solution of carriers to that of the water.

IR Analysis

The FTIR spectra of rivaroxaban, carrier, and their binary solid dispersions

(Spectrum BX) were captured by a Perkin Elmer FTIR spectrophotometer. Samples were mixed with spectroscopic grade potassium bromide and compressed into discs using a hydraulic press before being scanned from 4000 to 600 cm^{-1}. Data analysis software from Perkin Elmer was employed. (Spectrum V5.3.1).

Differential Scanning Calorimetry (DSC)

The thermal behaviour of rivaroxaban both alone and in actual physical combinations with tablet excipients was examined using DSC. Weighed and hermetically sealed samples (3-5 mg) were then heated at a constant rate of 10 °C/min between 25 °C and 250 °C. Sample thermograms were created using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software applications. Utilizing an Indian standard, the DSC temperature and enthalpy scales were calibrated. Nitrogen was used as the purging gas at a 30 mL/min flow rate.

Formulation of fast disintegrating Tablets

The chosen drug-poloxamer 188 solid dispersions were thoroughly mixed and lubricated with magnesium stearate before being put through filter no. 40. The powder mixture is directly crushed using 10 mm round concave punches on a rotary tableting equipment (Rimek small press, Karnavati Engineering Ltd., India) to create 200 mg tablets. The batches were created using a 2^3 factorial design with X1, X2, and X3 as the three independent variables. Where X1 is the Poloxamer ratio, X2 is the PEG 4000 content, and X3 is the PVP K30 content. For each component, two levels (-1, +1) were chosen to represent low and high values. Nine formulations, including the primary one, were created and their pre and post compression characteristics analyzed. Tables 3 and 4, respectively, provide the design pattern and component breakdown of 2^3 factorial designs of rivaroxaban IR formulations.

Precompression parameters

For all formulation batches, precompression variables including angle of repose, bulk density, tapped density, Carr's consolidation index, and Hausner's ratio were assessed in accordance with the recommended procedures.

Post compression parameters

Content uniformity test

Twenty tablets were chosen at random for this test, and each one was examined using a UV-Visible spectrophotometer at 248 nm. The acceptance value for this test must be within 15 % and the uniformity of the dose units must fall between 85 and 115 % of the specified range.

Hardness

The crushing strength (hardness) of samples of 10 crushed tablets for each tablet recipe was evaluated using a Monsanto hardness tester. For mechanical stability, a hardness of between 2 and 3 kg/cm^2 is deemed appropriate. Weight and SD average values were noted.

Friability test

Using a Roche friabilator (veego, VMP-D), the friability of the tablet was assessed. The initial weight (W0) and 20 pills were measured, weighed, and rotated at 25 rpm for 4 minutes (100 rotations in a Roche Friabilator) before being measured once again (W). As can be seen in the equation below, the percentage of friability was calculated using the weight loss. No more than 1% of total weight should be lost.

Friability (%) = [(Initial weight – Final weight) / (Initial weight)] ×100.

In vitro disintegration test

For this test, 900 ml of distilled water at 37 ± 0.5 °C was mixed with six pills of each formulation. Utilizing USP disintegration test equipment, the disintegration investigation was carried out in triplicate.

In vitro dissolution studies

The accurately weighed 10mg equivalent drug was taken for study and placed into the media, after which samples were collected using Whatman syringe filters-0.45 mm after successful collection of 6ml of sample. For this test, IP type-I (paddle method) was used at a speed of 50 rotations per minute, and the temperature of dissolution media using pH 6.8 phosphate buffer was maintained at 37 ± 0.5 °C with 0.5 % of sodium lauryl sulphate. Three times were run through this test (n=3) to determine the average percent cumulative drug release. [9,10]

Factorial design

The replies were assessed using an interactive and polynomial statistical model. Where B0 is the arithmetic mean of the eight runs' responses and Y is the dependent variable. The primary impacts show what happens when one element is raised from a low value to a high value on average. When two factors are adjusted at once, the reaction is illustrated by the interaction term. To examine nonlinearity, the polynomial terms have been included.

Optimized formulation selection

The most effective formulation was chosen using Design Expert software version 11. Software analysis was used to choose the optimized formulation in addition to the overall attractiveness value. Using the procedures described, it is proven that each response is personally desirable.

Differential scanning colorimetry (DSC)

It measures the alteration in physical characteristics brought on by a change in temperature; it is also known as a thermal analyser. All samples had to weigh less than 4 mg and be placed in an aluminium pan before being covered with an aluminium

lid. The DSC-4000, Perkin Elmer equipment was used to get the spectra, and the scanning was done at a rate of 10 °C/min from 50 °C to 300 °C. [11-14]

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

By analysing the thermal behaviour of the preparation, differential scanning calorimetry (DSC) was utilized to assess the melting point, crystallinity, breakdown, and drug-excipient interaction. By maintaining a heating rate of 1 °C/min, the DSC verified the presence of the medication rivaroxaban. Rivaroxaban's thermogram showed a pronounced endothermic peak with an onset temperature of 230.54 °C and a peak temperature of 233.19 °C, which is the same as its melting point.

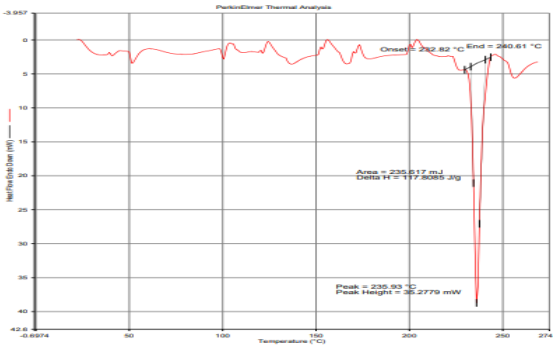

Fig 1: DSC-Rivaroxaban

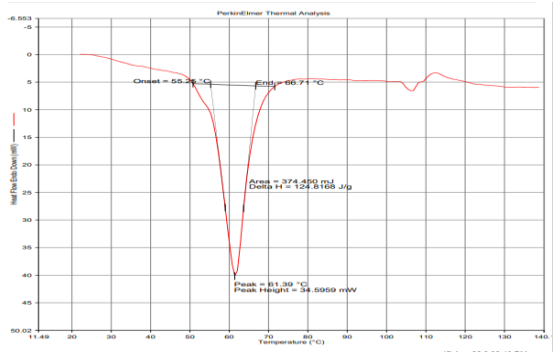

Fig 2: DSC- Poloxamer 188

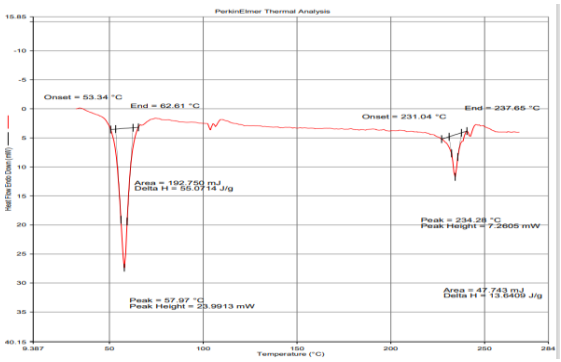

Fig 3: DSC-poloxamer 188 and rivaroxaban (M/F)

Solubility studies

The aqueous solubility of rivaroxaban in water is very low and is 25.05 mg/L at 25 °C. It increases with polymer and drug solid dispersions and is 20 mg/ml at 37± 0.5 ºC. Under phase solubility study of rivaroxaban, it was found that there is a significant increase in solubility with increased concentration of Poloxamer 188 and PVP K30. It has been noted that shelf polymeric conversion of the polymer plays a crucial part in the solid dispersions of the drug and the carrier.

Fourier-transform infrared spectroscopy (FTIR)

The FTIR spectra of rivaroxaban, polymer, and their solid dispersions were captured

using FTIR spectrophotometer. Samples were mixed with spectroscopic grade potassium bromide and compressed into discs using a hydraulic press before being scanned from 4000 to 600 cm^{-1}. Data analysis software from Perkin Elmer was employed. (Spectrum V5.3.1).

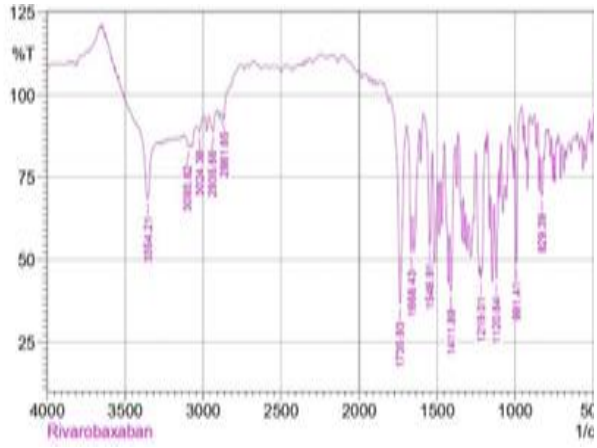

Fig 4: IR of rivaroxaban

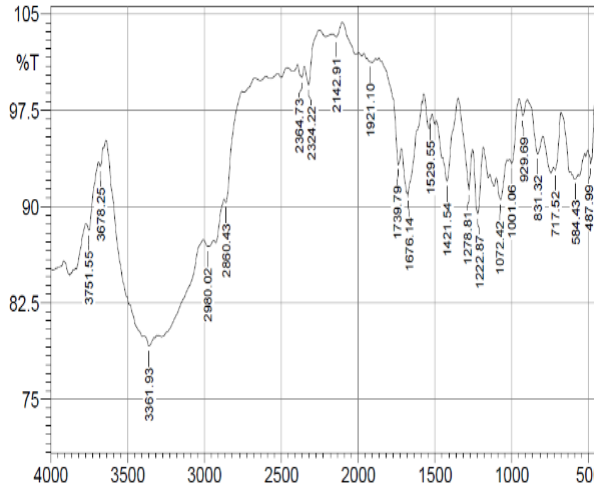

Fig 5: Rivaroxaban and PVP K30 solid dispersion.

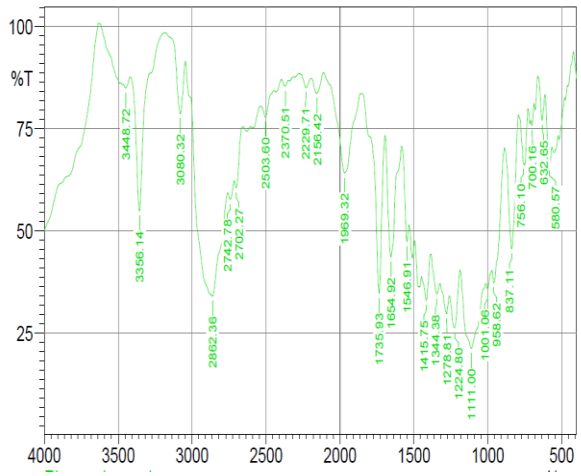

Fig 6: Rivaroxaban and poloxamer 188 solid dispersion.

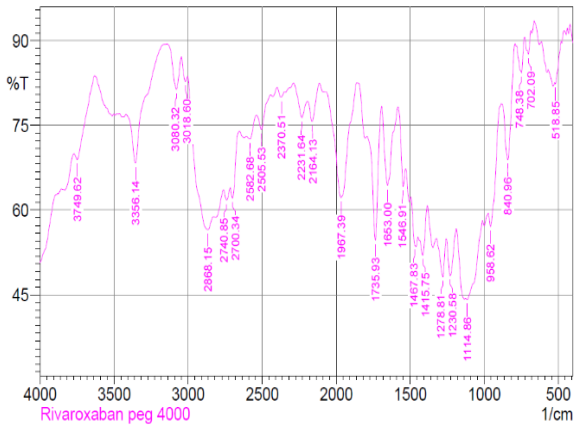

Fig 7: Rivaroxaban and PEG 4000 solid dispersion.

Precompression Parameters

The precompression properties of final active blends, including bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index, were examined; the findings are presented in the table below.

Table No. 1: Precompression Parameters

Sr. No.	Parameters	Observation
1	Bulk Density(g/ml)	0.692

2	Tapped Density(g/ml)	0.833
3	Compressibility Index (%)	16.93
4	Hausner's Ratio	1.204

Post-compression Parameters

Table 2 lists the outcomes of post-compression investigations. All eight formulations had content uniformity between 99.15 and 100.05. All eight formulations had identical dimensions. All eight formulations showed less than 1 % friability data, which suggested adequate abrasion resistance. The weight variation test was passed by all formulations. All formulations showed disintegration values less than 1 m. Disintegration is significantly influenced by PEG 4000. This might be as a result of swelling, which would cause the pill to break apart. The faster dissolving of tablets may be essential for the medicine to dissolve further. Higher PEG 4000 concentrations, however, do not promote the disintegration properties. Increased viscosity and cohesive effect between the particles may have contributed to the slower disintegration at higher PEG 4000 concentrations, which also delayed drug release.

Table No.: 2 Post-compression Parameters

Std	Run	Hardness (N)	% Drug Release	DT (min.)	CU (%)
2	1	2.6	94	4	99.15
5	2	2.7	92	2	99.43
4	3	2.5	98	3	99.67
3	4	2.7	93	3	99.73
1	5	2.6	93	3	99.32
8	6	2.5	98	1	99.34
6	7	2.7	96	2	99.57
7	8	2.6	94	1	99.74
9	9	2.6	99	1	100.05

***In vitro* drug release studies**

Displays the in vitro drug release for each of the eight formulations (F1-F9). The rate of medication dissolution was dramatically increased by adding solid dispersionsation and PEG 4000. There are several and poorly understood pathways for inclusion solid dispersions-derived dissolution enhancement. However, the major causes of the outcomes are thought to be better wettability, decreased aggregation and/or agglomeration, increased effective surface area, loss of drug crystallinity, and solubilization effects linked to the carriers. PEG 4000 was shown to improve the pace at which the medicine dissolves in tablets. The rate of rivaroxaban dissolution increased with PEG 4000 concentration. Due to the hydrophilic qualities of PEG 4000, the tablet had a greater wetting effect and had more surface area accessible for dissolving by lowering interfacial tension between the hydrophobic medication and the dissolution medium. For drugs and

formulations, the analysis of kinetic model fitting is conducted. Pure drug ranked first order model fitting shows that the drug dissolution is concentration dependant and happens via erosion controlled with n value of 0.695 (K-P model), exhibiting non Fickian diffusion. The formulations were ranked in the following order: Higuchi (explains drug release from polymer matrix), first order, zero order, Hixson-Crowell cube root rule. All formulations demonstrated Fickian diffusion except for the drug, which displayed first order and non-Fickian diffusion.

Factorial design

Table No.: 3 2^3 Full factorial design with central point and response

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:Poloxamer 188	B:PVP K30	C:PEG 4000	% Drug Release	Disintegration Time
2	1	60	8	10	94	4
5	2	20	8	14	92	2
4	3	60	12	10	98	3
3	4	20	12	10	93	3
1	5	20	8	10	93	3
8	6	60	12	14	98	1
6	7	60	8	14	96	2
7	8	20	12	14	94	1
9	9	40	10	12	100	1

Note: Run 9 is the central point in the 2^3 factorial design which shows the significant response

Responses

Table No.:4 Response of factorial design

Response	**Name**	**Observation**	**Analysis**	**Minimum**	**Maximum**	**Mean**	**Std. Dev.**	**Ratio**	**Transform**	**Model**
R1	% DR	8	Factorial	92	98	94.75	2.31	1.07	None	Main Effects
R2	DT	8	Factorial	1	4	2.38	1.06	4.00	None	Mean

ANOVA for selected factorial model

Response 1: % Drug Release

Table No.: 5 Response 1: % Drug Release

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	33.00	3	11.00	9.78	0.0259	significant

A-Poloxamer 188	24.50	1	24.50	21.78	0.0095	
B-PVP K30	8.00	1	8.00	7.11	0.0560	
C-PEG 4000	0.5000	1	0.5000	0.4444	0.5415	
Residual	4.50	4	1.13			
Cor Total	37.50	7				

Factor coding is coded. Sum of squares is Type III - Partial

The **Model F-value** of 9.78 implies the model is significant. There is only a 2.59% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

ANOVA for selected factorial model

Response 2: Disintegration Time

Table No.: 6 Response 2: Disintegration time

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	35.00	3	5.00	8.527	0.0259	significant
A-Poloxamer 188	21.50	1	21.50	21.32	0.0095	
B-PVP K30	8.00	1	8.00	7.11	0.0560	
C-PEG 4000	0.5000	1	0.5000	0.4444	0.5415	
Residual	4.50	4	1.13			
Cor Total	7.88	7				

Factor coding is coded**.** Sum of squares is Type III - Partial

Model terms are considered significant when the **P-value** is less than 0.0500. There are no important model terms in this instance. Model terms are not significant if the value is higher than 0.1000. Model reduction may enhance your model if it has a lot of unnecessary words (except those needed to maintain hierarchy).

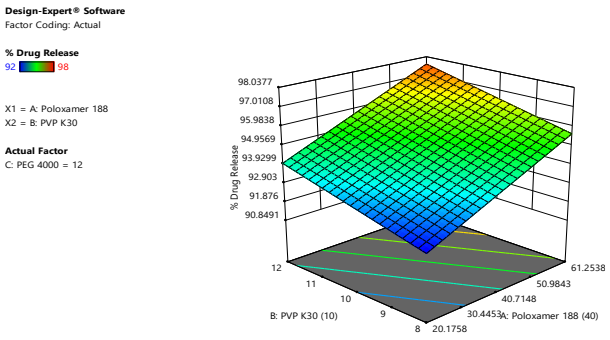

Fig. 8: % Drug release

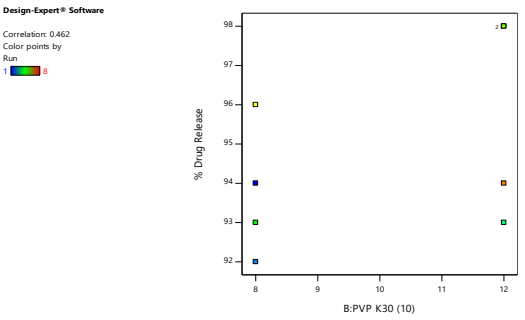

Fig. 11: % Drug release with PVP K30

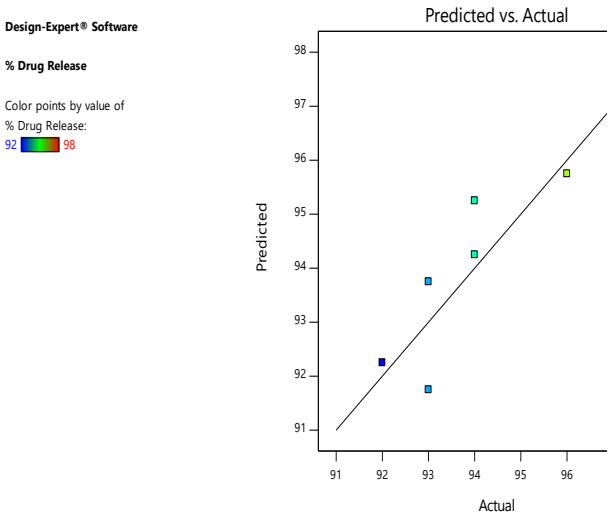

Fig. 9: % Drug release Predicted vs Actual

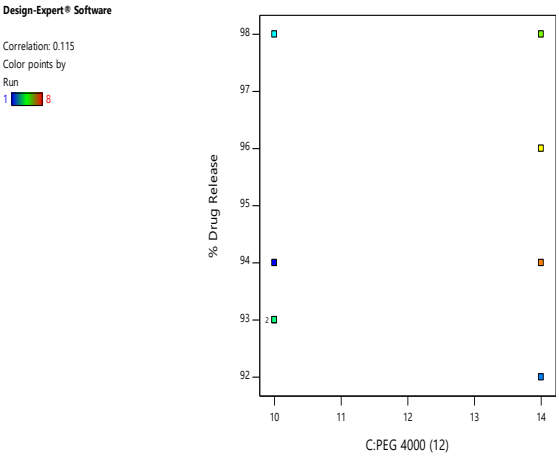

Fig. 12: % Drug release with PEG 4000

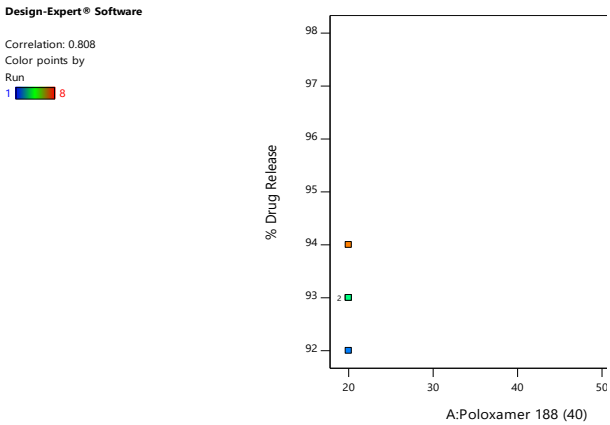

Fig. 10: % Drug release with Poloxamer 188

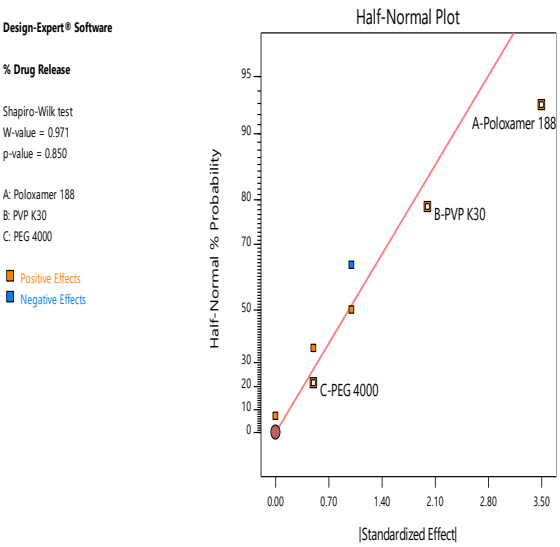

Fig. 13: Half Normal plot

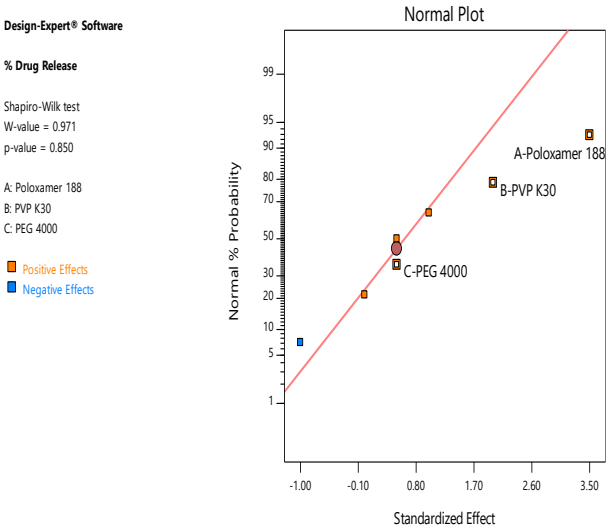

Fig. 14: Normal plot

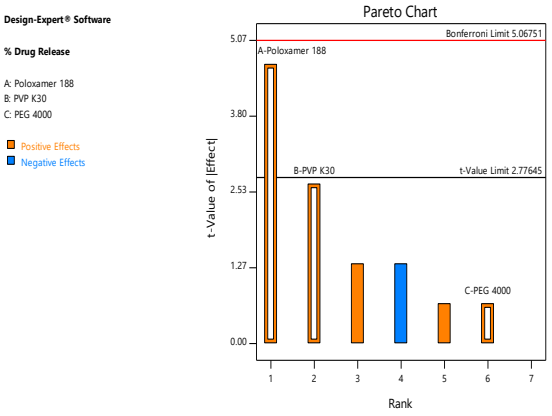

Fig. 15: Pareto Chart *In vitro* disintegration time (DT)

The statistical design's response may be used to explain the parameter disintegration time. The model is significant, according to the model's F value of 8.527. The DT of tablets was shown to be between 1 and 4 minutes. According to the polynomial equation, DT dropped as PVP K30 content increased. This may work by attracting water to the pill, which would then swell and break apart. The DT of the tablets may be important for the drug's later dissolution. The concentration of PEG 4000 was doubled, which further raised the DT of the tablets. The plastic nature of PEG 4000, which during compression might plasticize, soften, and partially plug the pores inside the tablets, could be a contributing factor to this outcome. This would result in the tablets having poor wettability capabilities. While PEG 4000 demonstrated binding abilities as well, utilizing higher amounts in tablets probably resulted in a slower rate of disintegration. With an increase in PVP K30 concentration, the DT of tablets reduced; this may be because to viscous networks.

***In vitro* drug release**

The F value of 9.78, which describes the parameter for in vitro drug release, tells us that with 40 mg of poloxamer, a large amount of drug has been dissolved. The model is significant (P 0.05), according to the model P value of 0.0259. Figure 5 displays a correlation diagram between actual and anticipated in vitro drug release values. The corrected R square of 0.9972 and the projected R square of 0.9985 accord rather well. Formulations are important model terms in this instance. Based on the polynomial equation, the effects of 3, 6, and 9 were agonistic. The range of in vitro tablet dissolution, from 93 to 98, suggested that drug release increased with increasing PEG 4000 content. The solubilization impact of the carrier and the improved

wettability/dispersibility of the medication after delivery are the two factors that contribute to the increased rate of rivaroxaban dissolution in the presence of PEG 4000. Improving medication solubility was the consequence of raising the concentration of PEG 4000 in formulations only to the optimal level, and subsequent increases in polymer concentration did not result in any further improvements. This might be explained by the viscous layer that developed surrounding the solid particles as a result of the greater PEG 4000 concentration, which decreased the diffusion coefficient and reduced drug solubility (according to the Stokes Einstein equation). The addition of PEG 4000 causes tablets to quickly dissolve, increasing the surface area and, as a result, the rate of dissolution. accelerated dissolution because compounds that are water soluble were formed. It is evident that the interactions between the hydrophobic component of the medication and a polar cavity result in the hydrophobic drug molecule becoming dehydrated and moving into the cavity, increasing its attraction for water and so accelerating dissolution. These results demonstrate that Poloxamer 188 has improved solubilizing and solid dispersions properties when PEG 4000 is added in tiny doses, which is further associated with higher drug release in the dissolving medium. According to the study, Poloxamer 188 and PEG 4000 are combined to produce inclusion solid dispersions. Table 3 displays several response parameters as well as a summary of regression analysis and ANOVA.

Formulation optimization using the desirability function

Finding the levels of the variable that influence the selected responses and figuring out the levels of the variable from which a strong product with high-quality properties may be generated are the fundamental steps in optimizing a pharmaceutical formulation. Three replies were used to compute the total desirability function, which was then compared to the desirability plot. Based on the outcomes and an overall desirability function, the formulation may be improved. Here, the formulation was optimized using the two answers of disintegration time and percentage of medication dissolved, which were fitted into the d1 and d2 scales of desirability, respectively. The results unmistakably point to formulation F9, which had the greatest attractiveness value of 0.85 and was regarded as the batch satisfying all the prerequisites for producing rivaroxaban tablets. Following examination, it was discovered that the formulation had a concentration of Poloxamer 188 and a quantity of PEG 4000 that met the strictest criteria for an ideal

formulation, with a P value of 0.0095. The findings of the desirability test showed that the estimated value and observed value did not differ significantly.

CONCLUSIONS

By forming compounds with Poloxamer 188, rivaroxaban's solubility and rate of dissolution can be improved. The rivaroxaban in the PEG 4000 tablet formulation was rapidly dissolved. The ideal formulations were chosen by P Value using response surface plots and contour plots created using Design Expert software. Multiple regression analysis was used to create mathematical polynomial models, which were found to be statistically significant (p 0.05) for a variety of response variables. The Design-Expert program chose Formulation F9 as the best candidate for formulation development since it had the best hardness, disintegration time, and in vitro drug release (98%) within 45 m. The rate of rivaroxaban dissolution increased as PEG 4000 concentration was raised to its ideal level. Due to the hydrophilic qualities of PEG 4000, the tablet had a greater wetting effect and had more surface area accessible for dissolving by lowering interfacial tension between the hydrophobic medication and the dissolution medium.

The percentage drug release was significantly impacted by poloxamer 188, according to the factorial design's co-efficient. The effects of the poloxamer and PEG 4000 combination in the rivaroxaban tablet were synergistic. Other poor water-soluble drug' dissolution rates can be increased using a similar strategy.

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