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Formulation and optimization of liquisolid tablet for improving the dissolution profile of rivaroxaban by using DoE approachand antithrombic activity

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ABSTRACT

Liquisolid technique is used in delivery of lipophilic and poorly water soluble drugs through oral route. It involves dissolving water insoluble drugs in nonvolatile solvents and converting into acceptably flowing and compressible powders. The present work was aimed to enhance the dissolution rate of Rivaroxaban by delivering the drug as a liquisolid compact. Liquisolid compacts were prepared using microcrystalline cellulose as the carrier and aerosil 200 as the coating material (R).PEG 400 was used as the liquid vehicle by studying the effect of the variable for response with the help of Box-Behnken design (BBD). A total of 17 formulations were prepared by altering the proportion of microcrystalline cellulose, aerosil 200 and PEG 400 by direct compression technique. The drug concentration was kept constant in all formulations at 50mg. Optimization was carried out using Box–Behnken design by selecting liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables; drug content and angle of repose were considered as dependent variables.The Fourier transform infrared (FTIR) and differential scanning calorimetry (DSC) studies revealed that there was no possible interaction between drug and tablet excipients. Prepared rivaroxaban liquisolid tablets were evaluated for thickness, hardness, weight variation, friability test, drug content, in-vitro dissolution studies, disintegration time, and stability studies. The optimized formulation yielded the response values, which were very close to the predicted values. Stability Study of optimized formula performed for 180 days at 30±2°C and 65±5% RH and 40^0C±2 ^{0}C and 75 ±5% RH

.Stability study performed on such parameters Color, Shape and Appearance. As a result there was no change seen at the end of the study. At the end drug content study of optimized formula performed and result shows that it was a stable formulation which was not degraded at different temperature and stable. *In-vivo* carrageenan induced antithrombic activity was performed on theSwiss albino rat (190-195±5gm). The results of our study suggest that formulation has significant effects against thrombosis. The mean length of the tail infracted region in the formulation- administered and heparin treated rat was shorter than that in the control rat. Typically, thrombosis occurs because of platelet aggregation or vasoconstriction, although platelet aggregation caused by cyclooxygenase inhibition has little or no effect on carrageenan-induced thrombosis in rat tails.

Keywords: *Rivaroxaban, Liquisolid technique, Liquid load factor, Non-volatile solvent, Carrier material, Coating material,Antithrombic activity*

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1. INTRODUCTION

As a most discussed but still not completely resolved issue, solubility or dissolution enhancement techniques remain the most vibrant field for the researchers in formulation science. Solubility and dissolution are the core concepts of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any medicine. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step of absorption of drugs from the gastrointestinal tract. As a result, more than 40% ofnew candidates entering drug development pipeline fail because of nonoptimal biopharmaceutical properties [1]. Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or

liquid lipophilic medication [2]. Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water soluble drugs [3-5]. The liquisolid technology is described by Spireas as liquid may be transformed into a free-flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. A liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug is formulated, it should be initially dissolved or suspended in suitable nonvolatile solvent system to produce drug solution or drug suspension of desired concentration. Inert, preferably water-miscible organic solvent systems with high boiling point and a not highly viscous organic solvent system such as propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or glycerine are best suitable as liquid vehicles [5]. The Rivaroxaban is selected as the API as it is a novel first oral anticoagulant drug. Rivaroxaban is used to prevent blood clots from forming due to a certain irregular heartbeat

(atrial fibrillation) or after hip or knee replacement surgery. It is also used to treat blood clots (such as in deep vein thrombosis-DVT or pulmonary embolus-PE) and to prevent the blood clots from forming again. Rivaroxaban has been shown more effective than the standard prescription of warfarin in reducing the like hood of ischemic strokes in patients with atrial fibrillation or abnormal heart rhythms. Rivaroxaban has poor water solubility and belongs to BCS Class II drugs [6]. Arterial thrombosis induced by platelet aggregation may cause life-threatening disorders such as unstable angina and reocclusion after angioplasty. Hence, inhibition of platelet aggregation is important in the prevention and treatment of cardiovascular diseases [7, 8]. Although certain pharmacological agents are effective in preventing the occurrence of the cardiovascular disorders, their safety cannot be guaranteed. During the initial stage of thrombosis, damage in blood vessels causes the production of adhesive proteins (such as collagen and von Willebrand factor) and soluble agonists (such as ADP and thrombin) at the injury site; this event then stimulates platelet adhesion, activation, and aggregation, resulting in the formation of a platelet-rich thrombus [9]. Activated platelets facilitate thrombin formation by providing a catalytic surface on which coagulation activation can occur. Thrombin not only is responsible for the formation of fibrin but also acts an extreme platelet activator. The growing mound of activated platelets is eventually stabilized by cross-linked fibrin and results in the formation of a platelet-rich thrombus [10, 11]. Therefore, the inhibition of platelet function is a promising approach for the prevention of thrombosis. In the present investigation, Rivaroxaban n a water insoluble drug was formulated into LS compacts using a liquid vehicle and studied for its pre- and postcompression parameters. Optimization of formulation was carried out using Box– Behnken design by selecting liquid load factor, amount of coating material and amount of magnesium oxide as independent variables and drug content, angle of repose as dependent variables and the effect of formulation variables was studied.

2. MATERIALS AND METHODS

Rivaroxabanwas a gift sample from Evonik Degussa India Pvt. Ltd., India. Micro crystalline cellulose was purchased from Yarrow Chem Products, Mumbai. Methanol and propylene glycol were purchased from Ranbaxy Fine Chemicals Ltd., New Delhi. Glycerin and aerosil 200 were purchased from Himedia Laboratories Pvt, Ltd., Mumbai. Crosscarmellose sodium was gifted from Anglo French Drugs and Industries. Ltd., Bangalore. Magnesium oxide was purchased

from NR Chem, Mumbai. Polyethylene glycol 400 (PEG 400) was purchased from E. Merck (India) Ltd., Mumbai. All other reagents and chemicals were of analytical grade.

Solubility study

A medicinal ingredient's solubility in water is a critical physical and chemical property that governs its systemic absorption and, as a result, its therapeutic efficacy. Saturation Shake-Flask (SSF) method was used for the determination of solubility. In this procedure, for the selection of best non-volatile solvent, pure drug was dissolved in different volatile and non-volatile solvents (acetonitrile (ACN), Methanol, DMSO and Dimethyl formamide) and distilled water. The sample was qualitatively tested for its solubility in various solvents. It was determined by shaking 2 mg of drug sample in 5 ml of solvent given in small test tube and observed to disappear the sample completely**.**

Drug excipient compatibility studies

The compatibility studies are carried out by Infrared spectroscopy (IR) and Differential scanning calorimetry, in order to evaluate the drug polymer interaction.

Fourier transform infrared studies

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in the formulation. FTIR spectra of pure Rivaroxaban and physical mixtures were obtained using PerkinElmer, Spectrum100. Samples are prepared in KBr disks (1mg sample in 100mg KBr). Spectrophotometer grade (in the range of 4000-400 cm-1).KBr was dried using IR lamp. Both KBr and drug was mixed and subjected to hydraulic pressure to form disc. This disc was placed in FT-IR chamber. Infrared spectrum was recorded in the 400-4000cm-1 and resolutionwas1cm-1.

Differential scanning calorimetry studies

DSC studies was performed using differential scanning calorimeter (Perkin Elmer Thermal Analysis) in order to assess the

thermal behavior of the Rivaroxaban and the liquisolid compacts prepared. The thermal behavior of the samples was investigated at a scanning rate of 20°C/min, covering a temperature range of 30–300°C [12].

Experimental design of rivaroxaban liquisolid compacts

The liquid load factor, amount of coating material, and amount of magnesium oxide as formulation variables, as well as the cumulative percentage drug release (100 percent) in minutes and angle of repose, were all considered when optimizing Rivaroxaban liquid solid compacts. To

evaluate the response variables, the experimental runs or formulation design were based on Box– Behnken designs and response surface methodology. Multiple regression analysis was performed on the responses to determine the relationship between the factors used and the results obtained. The liquid load factor, amount of coating material, and amount of magnesium oxide were chosen as independent variables for the analysis. The responses examined were cumulative percentage drug release and angle of repose. The effect of formulation variables on response variables was statistically evaluated using Design Expert 22.0.2.0trial version and one-way analysis of variance (ANOVA) at the 0.05 level (Stat Ease, USA).The design was evaluated using a quadratic model [12].The experimental runs are shown in Tables 1-3.

Method of preparation of liquisolid tablets

Using a rotary tablet press machine, rivaroxaban (1-17) liquidsolid systems were prepared and compressed into cylindrical tablets containing 50 mg of drug (Rimek Press, Ahmedabad).At different powder excipient ratios, all liquisolid formulations contained microcrystalline cellulose as the carrier and aerosil 200 as the coating material (R).PEG 400 was used as the liquid vehicle to prepare liquid medications.Different liquid load factors were used, as well as varying percentages of magnesium oxide as a flow activator. Finally, in all systems, 5% croscarmellose sodium was used as a disintegrant and magnesium oxide 1 % was used as a lubricant.Rivaroxaban was dispersed in PEG 400, and a mortar was used to add a mixture of microcrystalline cellulose and aerosil 200 while continuously stirring.Croscarmellose sodium and magnesium oxide were added to the preceding mixture, and the final powder blend was compressed with flat circular punches on a rotary tablet press machine [12].

Table 1: Composition of different variables used this formulation

S. No.	Run	Factor 1 A: Liquid load factor (ml)	Factor 2 B:Coating material (mg)	Factor 3 C: Mgo (%)
1	1	7.5	5	2
2	2	5	27.5	2
3	3	7.5	5	10
4	4	7.5	27.5	6
5	5	5	50	6
6	6	10	27.5	2
7	7	5	5	6
8	8	7.5	27.5	6
9	9	5	27.5	10
10	10	10	5	6
11	11	10	50	6
12	12	7.5	50	10
13	13	10	27.5	10
14	14	7.5	27.5	6
15	15	7.5	50	2
16	16	7.5	27.5	6
17	17	7.5	27.5	6

Table 1: Variables operating range for rivaroxaban liquisolid compacts

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Liquid load factor	is in range	5	10	1	1	3
B:Coating material	is in range	5	50	1	1	3
C:Mgo	is in range	2	10	1	1	3
Drug content	none	95.45	99.81	1	1	3
Angle of repose	none	24.76	31.76	1	1	3

Table 3: Formulation trials as per Box–Behnken design

S. No.	Run	Factor 1 A: Liquid load factor (ml)	Factor 2 B:Coating material (mg)	Factor 3 C: Mgo (%)	Response 1 Drug content (%)	Response 2 Angle of repose (Degree)
1	1	7.5	5	2	96.89	26.39
2	2	5	27.5	2	98.56	26.42
3	3	7.5	5	10	96.7	25.31
4	4	7.5	27.5	6	98.76	27.86
5	5	5	50	6	96.23	25.14
6	6	10	27.5	2	98.89	30.16
7	7	5	5	6	95.45	31.76
8	8	7.5	27.5	6	98.56	27.39
9	9	5	27.5	10	97.3	27.86
10	10	10	5	6	95.58	26.97
11	11	10	50	6	99.38	31.56
12	12	7.5	50	10	98.83	29.71
13	13	10	27.5	10	97.81	24.76
14	14	7.5	27.5	6	99.81	26.42
15	15	7.5	50	2	99.13	25.46
16	16	7.5	27.5	6	97.45	26.53
17	17	7.5	27.5	6	98.45	25.43

Pre and post compression studies of rivaroxaban liquisolid compacts

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. All the prepared liquisolid powders undergo the pre-compression studies such as

bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. The compressed liquisolid tablets of rivaroxaban were characterized for their for thickness, hardness, weight variation, friability test, drug content, in-vitro

dissolution studies, disintegration time, and stability studies [13].

Drug content

The total amount of drug present in the liquisolid formulation is evaluated using UV- visible spectrophotometric analysis. Liquisolidtablet which is dissolved in 0.01N of HCL and shaken for five minutes and finally 0.01N HCL was added to make the volume up to 100ml. The solution was then sonicated for 15 minutes and filtered through Whatman filter paper. Dilutions of the solution were prepared and the absorbance of resultant solution was measured spectrophotometrically at 248nm using UV/Visible spectrophotometer against 0.01N HCL as blank and drug content was calculated.

In-vitro dissolution studies

Dissolution studies were carried out by using USP type II apparatus (USP XXIII Dissolution Test Apparatus) using 900 ml of phosphate buffer pH 7.4 as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 2°C. Aliquots of sample (2 ml) were withdrawn from the dissolution apparatus at regular predetermined time intervals and the samples were replaced with fresh dissolution medium. Absorbance of the collected samples after suitable dilution with phosphate buffer pH 7.4 was measured at 248 nm by using UV/ Visible Spectrophotometer. Percentage of drug released was calculated from the standard calibration curve [14].

Disintegration time

A Disintegration Tester was used to measure the disintegration time of the tablets, in accordance with USP30. Disintegration procedures for the tablets using 900 ml of media at 37°C. Six tablets were dropped into individual tubes of the basket-rack assembly. Disks were not mounted on the tubes and the time at which all six tablets had disintegrated was recorded.

Stability studies

The tablet formulations were packed in aluminum foil and were placed in the stability test chamber and subjected to stability studies at accelerated testing 30±2°C/65±5% RHand 40±2°C/75±5%RH for 6 months. The tablets were checked for physical appearance, hardness, and friability and drug content and in-vitro dissolution studies at the interval of 2 months. The

shelf life was predicted by using similarity factor (f2) analysis according to International Conference on Harmonisation (ICH) guidelines [15].

In-vivo carrageenan induced rat antithrombic activity Animals

Swiss albino rat (190-195±5gm) was obtained from Pinnacle Biomedical Research Institute, Shamla Hills Bhopal. Animals were maintained in a room with controlled temperature (22±2

°C) for 12 h light/12 h dark cycle with free access to food and water. Animal care and research protocols were based on the principles and guidelines adopted CPCSEA and approved by the Institutional animal ethical committee.

Methods

The in vivo thrombolytic activity of formulation was assessed in the carrageenan-induced thrombosis rat model. Group 2 consist of 1 mg/kg of carrageenan were dissolved in 1X phosphate-buffered saline (50 mmol/L Sodium phosphate buffer, 100 mmol/L NaCl, pH 7.4) and administrated intravenously in the tail vein of rats. Group 1the control group was administered only saline. The animals were observed after 24 hours for thrombus formation in the tail. The animals in treatment groups 4 and 5 were treated with 20mg/kg Rivaroxaban (RVRX) and 25 mg/kg formulation dissolved in 20% DMSO. Groups 3 were respectively injected with 100 IU heparin sodium as positive controls i.p.

3. RESULTS AND DISCUSSION

The solubility of Rivaroxaban was determined in various volatile and non-volatile liquid vehicles such as Dimethyl sulfoxide, Dimethyl formamide, Acetonitrile, Methanol and Water shown in Table 4. From the results, it was observed that the drug is freely soluble in acetonitrile, Dimethyl sulfoxide, and Dimethyl formamide, sparingly soluble in water and slightly soluble in methanol. IR spectrum of rivaroxaban was interpreted and the functional groups were identified. The first peak was found at 3355.32 cm^{-1}which confirmed the presence of amide group. Aromatic alkane (C-H) stretching peak and in ring peak were identified at 3067.98 cm^{-1} and 1606.14 cm^{-1} respectively. Alkane (C-H) stretching peak was found at 29366.28 cm^{-1}. Free amide (C=O) stretching peak was found at 1737.02 cm^{-1}. Associated amide (C=O) stretching peak was found at 1606.14 cm^{-1}. Aromatic ester (C-O) stretching peak was identified at 1285.86 cm^{-1}. Aliphatic amines (C-N) stretching peak was found at 1145.76 cm^{-1}. Aliphatic ether (C-O) stretching peak was found at 1077.95 cm^{-1}. Aromatic sulfur (C-S) stretching peak was found at 991.69 $cm^{-1}$and

halo compound (C-Cl) stretching peak was found at 845.85 cm^{-1}.The FTIR spectra of rivaroxaban confirmed the presence of the main functional group such as amide, alkane, ester, sulfur etc (Figure 1a). Similar absorption peaks were observed in the IR spectra of physical blend of drug and excipients [Figures 1b-d], showed that there was no shift or disappearance

of the characteristic parameter prelated to and was very much in conformity with the standard reference spectra, but with lower intensity substantiating the compatibility of the drug and the polymers used. Figure 2 revealed the thermal behaviors of the pure drug together with the thermal behavior of the physical mixture of rivaroxaban and excipient. Rivaroxaban [Figure 2a] demonstrated a sharp characteristic endothermic peak around at 230°C corresponding to its melting temperature, which signified that rivaroxaban was in pure crystalline state. The DSC thermo gram of physical mixture in Figure 2b showed an endothermic peak at around 120°C. These studies confirmed that there was no change in crystallinity and there was no interaction between the drug and excipients in the Formulation. The bulk density of various formulations were found to be between 0.31- 0.39, tapped density between 0.40-0.44, Hausner's ratio between 1.12- 1.287, Carr's index between 16.3- 19.7 which shows the good compressibility index of formulations.The angle of repose was found to be between 25.14 -31.76^0, which shows the excellent flow properties of formulation. Results of measurements such as Tapped density, Angle of repose, Carr's index, Hausner's ratio are presented in the Table 5. All prepared tablets complied with the pharmacopoeial required specifications for physical properties of liquisolid compacts. Results of hardness, friability, and disintegration time are represented in Table-6. Hardness test showed hardness of liquisolid tablets ranging from 3.5-4.0 Kg/cm^3. Another measure of tablets strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was <1%, indicating that the friability is within the prescribed limits. This indicates acceptable resistance was shown by liquisolid tablets to withstand handling. Disintegration time was found to be in the range of 70-

85 seconds for liquisolid preparations intended for immediate drug release characteristics. Tablets of different formulations were evaluated for the post-compressional parameters such as general appearance, weight variation, hardness, thickness, friability, and drug content for tablets Table 6. The experimental nature based on this mixture of the component has resulted in 17 separate formulation batches (counting center points in construction). As indicated, numerous formulation lots were prepared and then assessed for each of the responses. The significance of

the model with that of comparing with the other model for the analysis by analysis of variance (ANOVA). In polynomial equations, positive sign before the factor shows the linear correlation between response and factor, while the negative sign shows the inverse relation between the same. All the responses recorded for 17 runs and the relation of independent and dependent variables are presented in Table 2 and 3. Optimization was carried out by Box–Behnken design employing response surface methodology by taking into consideration liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables and the influence of these variables on the responses, drug content and angle of repose respectively. The Box– Behnken design was adopted to analyze the relationships between multiple variables with a reduced number of experimental runs. According to this design, 17 formulations were prepared as mentioned in Table 2. Selection of working method was done on the basis of drug content and angle of repose. A factorial design was used to study the effect of Independent variables on the dependent variables. The Model F-value of 4.71 implies the model is significant. There is only a 2.67% 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 B, B² are significant model terms. 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. The Lack of Fit F-value of 0.55 implies the Lack of Fit is not significant relative to the pure error. There is a 67.27% chance that a Lack of Fit F-value this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit Table 7. The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi- colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable. The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients Table 8. The results of formulations as per the design when fitted into various models, a linear model was found to be significant for drug content with F value of 4.71 and P value 0.0267. In this model factors A and

B (liquid load factor and amount of aerosil 200) significantly affected the drug content, where as factor C (amount of magnesium oxide) do not have significant effect on the response. The model equation is as follows: Drug content=+98.61 + 0.5150 A + 1.12 B – 0.3537 C + 7550 AB + 0.0450 AC – 0.0275 BC – 0.0275 BC – 0.8468 A^2 -1.10 B^2 + 0.3808C^2. The effect of both the

factors A and B can be explained with the help of the 3D response surface plot as shown in Figure 3. As the liquid load factor and concentration of aerosil increased, the drug content increased. The Model F-value of 3.23 implies the model is significant. There is only a 4.96% 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 AB 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. The Lack of Fit F-value of 4.32 implies there is a 8.92% chance that a Lack of Fit F-value this large could occur due to noise. Lack of fit is bad -- we want the model to fit. This relatively low

probability (<10%) is troubling Table 9. The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings. When the factors are orthogonal the VIFs are 1; VIFs greater than 1 indicate multi-colinearity, the higher the VIF the more severe the correlation of factors. As a rough rule, VIFs less than 10 are tolerable Table 10. The results of formulations as per the design when fitted into various models, quadratic model was found to be significant for angle of repose with F value 3.23 and P value0.0500. In this model factor B (amount of aerosil200) significantly affected the angle of repose, whereas, the factors A and C (liquid load factor and amount of magnesium oxide) do not have significant effect on angle of repose. The model equation is as follows: Angle of repose = +27.36 + 0.2838 A + 0.1800 B – 0.0988 C + 2.80 AB – 1.71 AC + 1.33 BC. The effect of factor B can be explained with the help of the 3D response surface plot as shown in Figure 4. As the concentration of aerosil increased, the angle of repose of the liquid solid compacts increased. The results of ANOVA are shown in Table 9 .The results when analyzed and optimized had generated numerical optimized solutions based on these experimental design. From the numerical optimization results, a solution was selected randomly, coded as optimized formulation and considered as optimized liquid solid compact formulation. The results of predicted observation and actual experimentation are shown

in Table 9 which confirmed the closeness of the predicted results with that of the observed results and it was observed that the response was almost similar to the response predicted by the software Figure 4. The Model F-value of 3.23 implies the model is significant. There is only a 4.96% 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 AB 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. The Lack of Fit F-value of 4.32 implies there is a 8.92% chance that a Lack of Fit F-value this large could occur due to noise. Lack of fit is bad -- we want the model to fit. This relatively low probability (<10%) is troubling Table 11. The bulk density of the optimized powder blend was found to be0.344gm/cm^3. The tapped density of the powder blend was 0.443gm/cm3. The Carr's index of the formulation was found to be in 16.335. It was less than 25%, which indicates that the powder blend have required flow property for compression of tablets. The Hausner's ratio of the formulation was found to be1.136, the angle of repose is a characteristic of the internal friction or cohesion of the particles, the value will be low, if the powder is non-cohesive and high if the powder is cohesive. Prepared optimized formulation was in the range of 27.76, which indicates the good flow properties of liquisolid powder Table 12. Optimized formulation were evaluated for the post-compressional parameters such as general appearance, weight variation, hardness, thickness, friability, disintegration time and drug content for tablets Table

13. *In- vitro* drug release study of optimized formulation was performed with the help of dissolution apparatus (USP –II, SV scientific). Results of this study reveal that the optimized formula shows the 98.58 percent of release of drug at 50 min. For kinetic study following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (Higuchi model); log cumulative % drug release vs. log time (Korsmeyer–Peppas model).As a result zero order kinetic models shows the regression $R^2 = 0.947$, first order kinetic model shows the regression $R^2 = 0.835$, Higuchi model shows the regression $R^2 = 0.974$ and Korsmeyer–Peppas model shows the regression $R^2 = 0.792$. The In-vitro drug release data for optimized formulation was performed in pH phosphate buffer 7.4. The optimized formulation showed 98.58 %drug release within 50min, which correlated with the predicted data.In the above table 37 R2 is correlation value. On the basis of best fit with the highest correlation (R2) value it

is concluded that in the optimized formulation of liquisolid tablet follow the Highuchi kinetic model Table 14, 15 & Figure 5-8. The selected optimized formulation was evaluated for stability studies which were stored at temperature of 30±2°C and 65±5% Relativehumudity and 40^0C±2 ^{0}C and 75 ±5%Realative humidity for 180 days (6 month) and were analyzed for their assay, Physical appearance, In vitro dissolution study and drug content study. There was no significant change in the physicochemical properties of optimized formulation during the stability period. It was well within the acceptable limit Table 16-18. Carrageenan-induced tail thrombosis model is one of the models that have been used to evaluate antithrombotic and thrombolytic agents, such as heparin. It allows observing the progression of thrombosis visually and directly in a time-dependent manner. Swelling and redness were observed within 2–3 h after intravenous injection of carrageenan, and the tail appeared black after 6 h, indicating that thrombosis had formed in the tail. Measurement of the length of black tail (thrombosis) was carried out at 24, 48, and 72 h after injection. The results of our study suggest that Formulation has significant effects against thrombosis. The mean length of the tail infracted region in the Formulation-administered and heparin treated rat was shorter than that in the control mice. Typically, thrombosis occurs because of platelet aggregation or vasoconstriction, although platelet aggregation caused by cyclooxygenase inhibition has little or no effect on carrageenan- induced thrombosis in rat tails Table 19.

Table 4: Determination of solubility of rivaroxaban in different solvents

S.No.	Solvents	Solubility
1.	Dimethyl sulfoxide	Freely soluble
2.	Dimethyl formamide	Freely soluble
3.	Acetonitrile	Freely Soluble
4.	Water	Soluble
5.	Methanol	Slightly soluble

Table 5: Result of pre-compressional evaluation of liquisolid system

Formulation	Bulk density(g/cm3)	Tapped density(g/cm3)	Hausner's ratio	Carr's ratio%	Angle of repose
F1	0.313	0.432	1.178	19.341	26.39
F2	0.323	0.411	1.231	17.254	26.42
F3	0.343	0.428	1.152	17.345	25.31
F4	0.363	0.410	1.321	16.547	27.86
F5	0.359	0.432	1.264	16.981	25.14
F6	0.330	0.407	1.231	17.214	30.16
F7	0.344	0.443	1.136	16.335	27.76
F8	0.335	0.403	1.287	16.173	27.39
F9	0.329	0.410	1.272	18.076	27.86
F10	0.349	0.440	1.247	17.268	26.97
F11	0.329	0.432	1.129	16.569	31.56
F12	0.351	0.411	1.203	16.465	29.71
F13	0.330	0.428	1.233	17.266	24.76
F14	0.360	0.463	1.224	19.780	26.42
F15	0.375	0.479	1.234	17.622	25.46
F16	0.396	0.456	1.246	17.203	26.53
F17	0.394	0.434	1.276	19.763	25.43

Table 6:Result of post-compressional evaluation of liquisolid tablet

Formulation	Thickness (mm)	Hardness Kg/cm^3	Friability (%)	Weight variation (mg)	% Drug content	Disintegration time (sec)
F1	4.01±0.04	3.8±0.057	0.74±0.026	199.42	96.89	80.86±2.88
F2	3.28±0.038	3.5±0.076	0.75±0.026	200.14	98.56	73.66±8.14
F3	3.50±0.017	3.5±0.104	0.76±0.019	199.23	96.70	72.66±1.23
F4	3.70±0.019	3.8±0.0288	0.76±0.019	201.53	98.76	73.00±3.0
F5	4.01±0.04	4.0±0.05	0.71±0.057	200.14	96.23	85.00±1.52

F6	3.28±0.038	3.0±0.057	0.69±0.076	198.60	98.89	76.33±5.30
F7	3.50±0.017	3.7±0.05	0.75±0.057	200.78	99.07	66.00±2.51
F8	3.70±0.019	4.0±0.076	0.72±0.076	199.58	98.56	80.86±2.88
F9	3.36±0.026	3.8±0.057	0.71±0.057	200.56	97.30	83.66±8.14
F10	4.01±0.031	3.5±0.076	0.68±0.026	198.84	95.58	82.66±1.23
F11	4.01±0.04	3.5±0.104	0.68±0.104	201.63	98.38	63.00±3.0
F12	3.28±0.038	3.8±0.0288	0.71±0.026	197.53	98.83	85.00±1.52
F13	3.50±0.017	4.0±0.05	0.72±0.017	202.07	97.81	76.33±5.30
F14	3.70±0.019	3.0±0.057	0.760.0288	201.36	95.81	66.00±2.51
F15	3.36±0.026	3.5±0.05	0.73±0.057	198.23	99.13	80.86±2.88
F16	2.1±0.01	4.0±0.076	0.72±0.05	200.56	97.45	83.66±8.14
F17	2.2±0.02	3.8±0.057	0.71±0.057	200.78	98.45	72.66±1.23

Table 7: Response 1: Drug content (ANOVA for Quadratic model)

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	24.28	9	2.70	4.71	0.0267	significant
A-Liquid load factor	2.12	1	2.12	3.70	0.0958	
B-Coating material	10.01	1	10.01	17.46	0.0041	
C-Mgo	1.00	1	1.00	1.75	0.2279	
AB	2.28	1	2.28	3.98	0.0864	
AC	0.0081	1	0.0081	0.0141	0.9087	
BC	0.0030	1	0.0030	0.0053	0.9441	
A^2	3.02	1	3.02	5.27	0.0554	
B^2	5.09	1	5.09	8.87	0.0205	
C^2	0.6104	1	0.6104	1.06	0.3365	
Residual	4.01	7	0.5734			
Lack of Fit	1.18	3	0.3925	0.5536	0.6727	not significant
Pure Error	2.84	4	0.7090			
Cor Total	28.30	16				

Table 8: Coefficients in terms of coded factors

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	98.61	1	0.3386	97.81	99.41	

A-Liquid load factor	0.5150	1	0.2677	-0.1180	1.15	1.0000
B-Coating material	1.12	1	0.2677	0.4857	1.75	1.0000
C-Mgo	-0.3537	1	0.2677	-0.9868	0.2793	1.0000
AB	0.7550	1	0.3786	-0.1403	1.65	1.0000
AC	0.0450	1	0.3786	-0.8503	0.9403	1.0000
BC	-0.0275	1	0.3786	-0.9228	0.8678	1.0000
A^2	-0.8468	1	0.3690	-1.72	0.0258	1.01
B^2	-1.10	1	0.3690	-1.97	-0.2267	1.01
C^2	0.3808	1	0.3690	-0.4918	1.25	1.01

Table 9: Response 2: Angle of repose (ANOVA for 2FI model)

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p- value**	
Model	51.20	6	8.53	3.23	0.0496	significant
A-Liquid load factor	0.6441	1	0.6441	0.2436	0.6323	
B-Coating material	0.2592	1	0.2592	0.0980	0.7606	
C-Mgo	0.0780	1	0.0780	0.0295	0.8670	
AB	31.42	1	31.42	11.88	0.0063	
AC	11.70	1	11.70	4.42	0.0617	
BC	7.10	1	7.10	2.69	0.1323	
Residual	26.44	10	2.64			
Lack of Fit	22.90	6	3.82	4.32	0.0892	not significant
Pure Error	3.54	4	0.8846			
Cor Total	77.64	16				

Table 10: Coefficients in terms of coded factors (angle of repose)

Factor	**Coefficient Estimate**	**df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	27.36	1	0.3944	26.48	28.24	
A-Liquid load factor	0.2838	1	0.5749	-0.9972	1.56	1.0000
B-Coating material	0.1800	1	0.5749	-1.10	1.46	1.0000
C-Mgo	-0.0988	1	0.5749	-1.38	1.18	1.0000

AB	2.80	1	0.8131	0.9909	4.61	1.0000
AC	-1.71	1	0.8131	-3.52	0.1016	1.0000
BC	1.33	1	0.8131	-0.4791	3.14	1.0000

Table 11: Solutions found

Number	Liquid load factor	Coating material	Mgo	Drug content	Angle of repose	Desirability	
1	8.030	8.520	7.900	96.750	26.015	1.000	
2	5.000	27.500	10.000	97.226	28.688	1.000	
3	10.000	27.500	2.000	98.964	29.453	1.000	
4	7.500	5.000	2.000	97.095	28.612	1.000	
5	10.000	5.000	6.000	95.301	24.662	1.000	
6	10.000	27.500	10.000	98.346	25.836	1.000	
7	7.500	50.000	2.000	99.388	26.307	1.000	Selected
8	7.500	5.000	10.000	96.442	25.749	1.000	
9	5.000	5.000	6.000	95.781	29.699	1.000	
10	5.000	50.000	6.000	96.509	24.454	1.000	
11	10.000	50.000	6.000	99.049	30.627	1.000	
12	7.500	50.000	10.000	98.625	28.774	1.000	
13	5.000	27.500	2.000	98.024	25.466	1.000	
14	6.380	43.907	7.034	98.113	26.873	1.000	
15	9.674	29.265	2.978	99.003	28.932	1.000	
16	6.403	35.636	6.845	98.294	27.096	1.000	
17	5.216	41.346	7.271	97.184	26.362	1.000	

Table12: Result of pre-compressional parameter of optimized formulation

S No.	Parameter	Values
1.	Bulk density (g/ml)	0.344
2.	Tapped density (g/ml)	0.44
3.	Carr’s index (%)	16.335
4.	Hausner’s ratio	1.136
5.	Angle of repose	27.76

Table 13:Post-compressional evaluation of optimized liquisolid tablets

S.No	Parameter	Results
1.	Colour	White in colour
2.	Shape	Round

3.	Appearance	Elegant
4.	Thickness (mm)	3.50±0.017
5.	Hardness	3.7±0.05
6.	Friability (%)	0.75±0.057
7.	Weight variation (mg)	200.78
8.	% Drug content	99.07

Table 14: In- vitro drug dissolution study of optimized formulation

S. No	Time (Min.)	cumulative % drug released	% drug remaining	log Cumu % drug remaining	log Cumu % drug released	log time
1.	0	0	100	2.000	0.000	0.000
2.	10	27.5	72.59	1.878	1.388	0.301
.	20	42.52	57.45	1.704	1.694	0.602
4.	30	62.5	37.52	1.566	1.801	0.778
5.	40	84.55	15.4	1.412	1.870	0.903
6.	45	92.6	7.4	1.225	1.920	1.000
7.	50	98.58	1.42	-0.056	1.996	1.079

Table 15: Result of correlation value (R^2 value)

Formulation	Model	Kinetic parameter values
Tablet	Zero Order	$R^2 = 0.947$
	First Order	$R^2 = 0.835$
	Higuchi	$R^2 = 0.974$
	Korsmeyerpeppas	$R^2 = 0.792$

Table 16: Physical appearance in different temperature and RH

S. No	Time (Days)	30±2°C and 65±5% RH			40^{0}C±2 ^{0}C and 75 ±5% RH		
		Colour	Shape	Appearance	Colour	Shape	Appearance
1.	0	White in colour	Round	Elegant	White in colour	Round	Elegant
2.	30	White in colour	Round	Elegant	White in colour	Round	Elegant
3.	60	White in colour	Round	Elegant	White in colour	Round	Elegant
4.	120	White in colour	Round	Elegant	White in colour	Round	Elegant

5.	180	White in colour	Round	Elegant	White in colour	Round	Elegant

Table 2: Result of *In vitro* dissolution study for 6 months

S. No	Time (Min.)	0 Days	30Days	60 Days	120 Days	180 Days
1.	0	0	0	0	0	0
2.	10	24.41	24.42	24.39	24.38	24.35
3.	20	49.45	49.44	49.46	49.45	49.47
4.	30	63.18	63.20	63.17	63.16	63.19
5.	40	74.20	74.19	74.26	74.22	74.15
6.	45	83.20	83.14	83.19	83.09	83.10
7.	50	98.58	98.56	98.55	98.54	98.53

Table 3: Result of drug content in different temperature and RH

S.No	Time (Days)	30±2°C and 65±5% RH	40^0C±2 ^{0}C and 75 ±5% RH
		Drug content	Drug content
1.	0	98.58	98.59
2.	30	98.57	98.56
3.	60	98.55	98.54
4.	120	98.54	98.53
5.	180	98.53	98.53

Table 19: Results of antithrombic activity

Group	Treatment	Length of tail thrombosis (mm)		
		24 hr	48 hr	72 hr
Group I	Normal	-	-	-
Group II	Carrageenan	39.50 ± 4.764	41.66 ±5.240	43.00 ±5.138
Group III	Heparin	23.00 ±1.788**	23.83 ±1.471**	22.66 ±1.632**
Group IV	Rivaroxaban	25.16 ±1.169**	24.66 ±1.505**	24.00 ±2.00**
Group V	Formulation	24.00 ±0.894**	24.00 ±1.549**	23.83 ±1.471**

Values are expressed as MEAN±SD at n=6, One-way ANOVA followed by Bonferroni test, **P<0.001 and ^{NS}P>0.001 compared to the Carrageenan treated group.

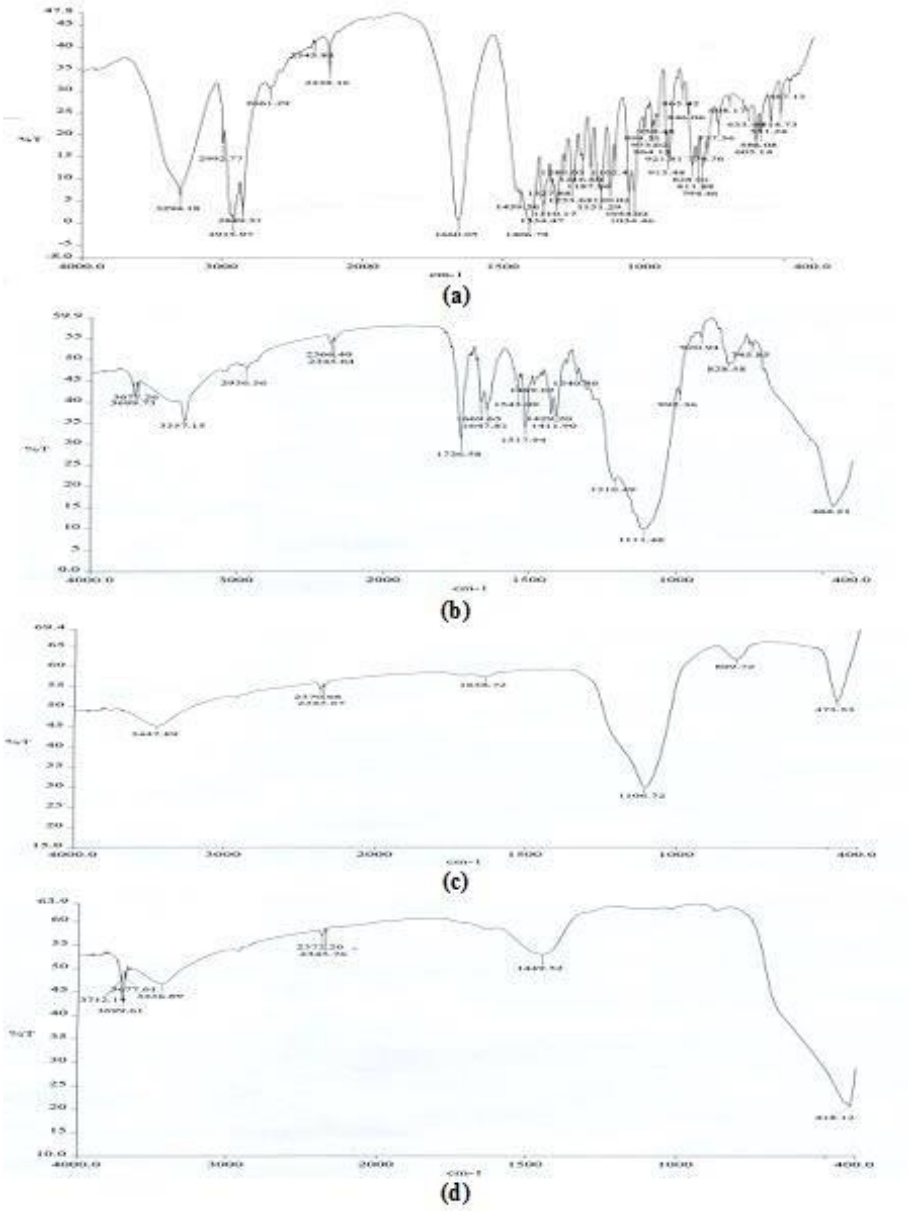

Figure 1: Infra red spectrum of rivaroxaban. (a) Infra red spectrum of rivaroxaban and excipients. (b) Infra red spectrum of aerosil 200 (c). (d) Infra red spectrum of magnesium oxide

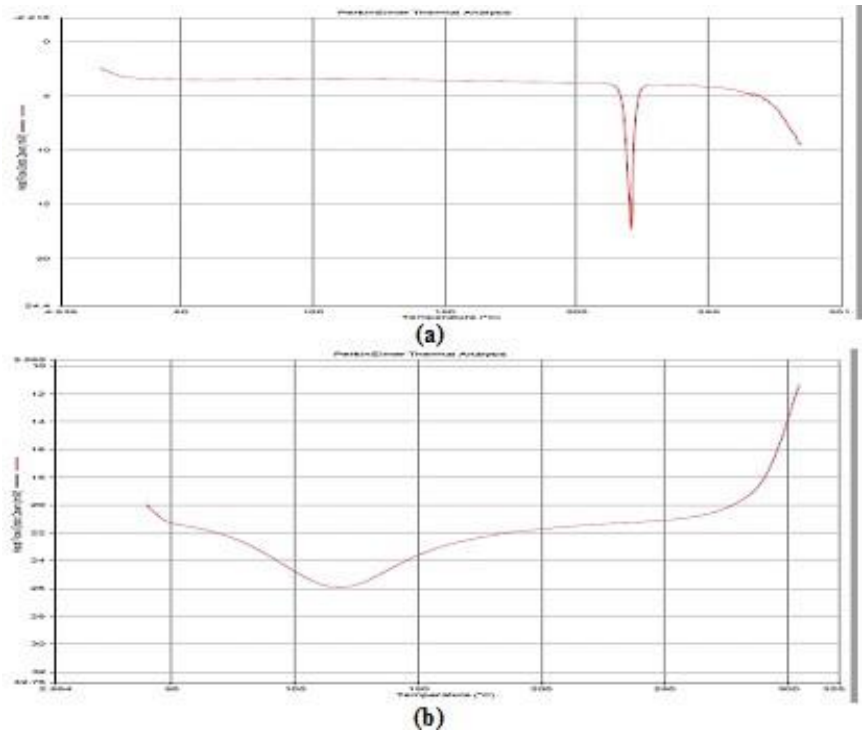

Figure 2: DSC thermograms of rivaroxaban. b)DSC thermogram of physical mixture of ketoprofen and excipients

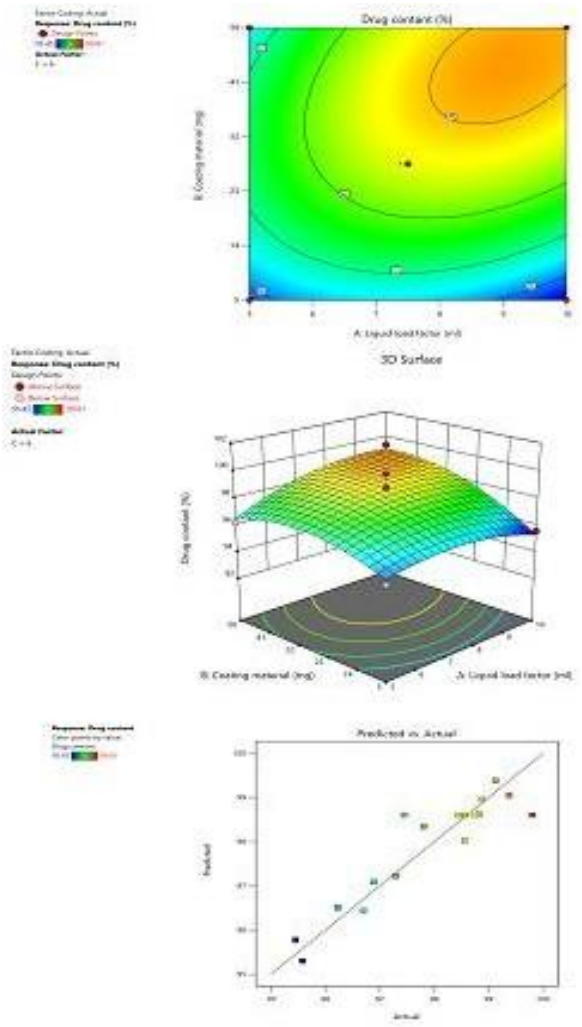

Figure 3: Response surface plot showing combined effect of liquid load factor abd coating material on drug content of formulation

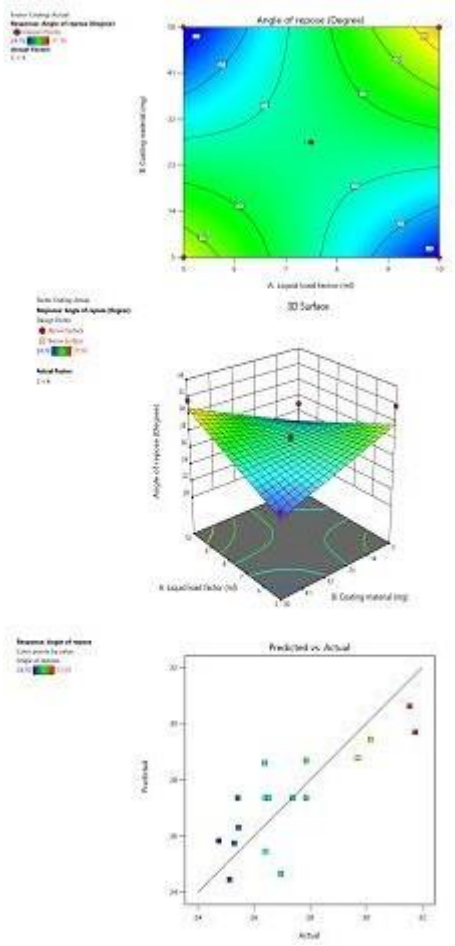

Figure 41: Response surface plot showing combined effect of Liquid load factor and coating material on angle of repose of formulation

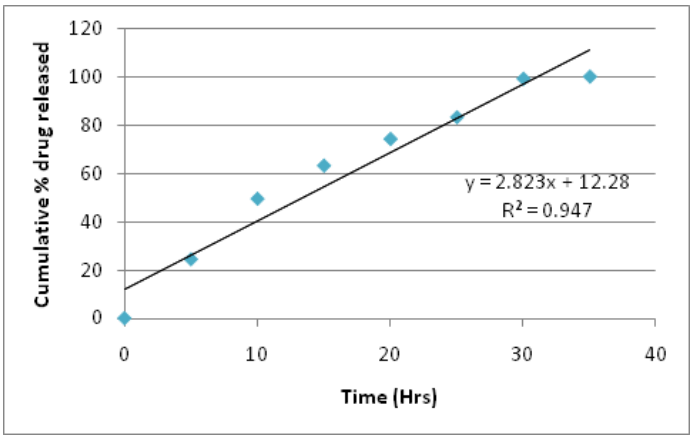

Figure 2: Zero order kinetic model

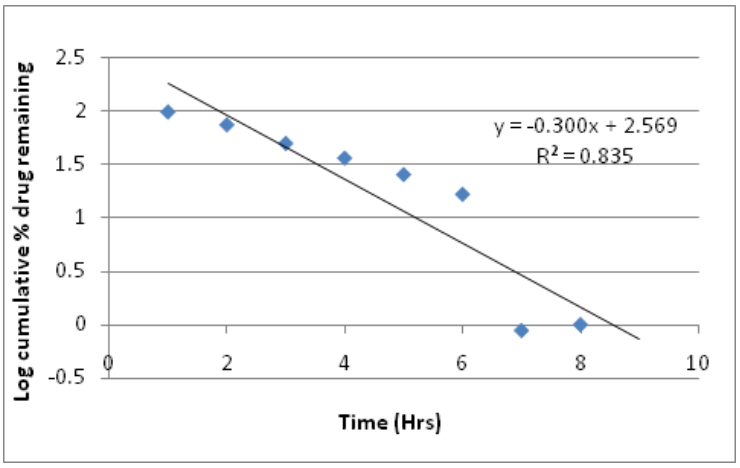

Figure 6: First Order kinetic model

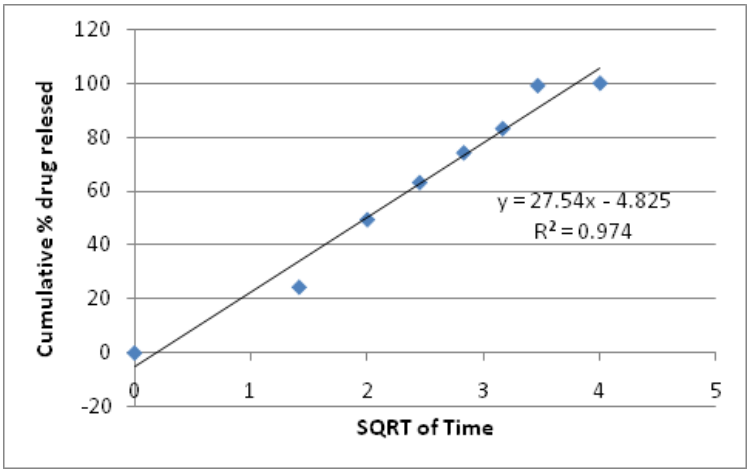

Figure 7: Higuchi model

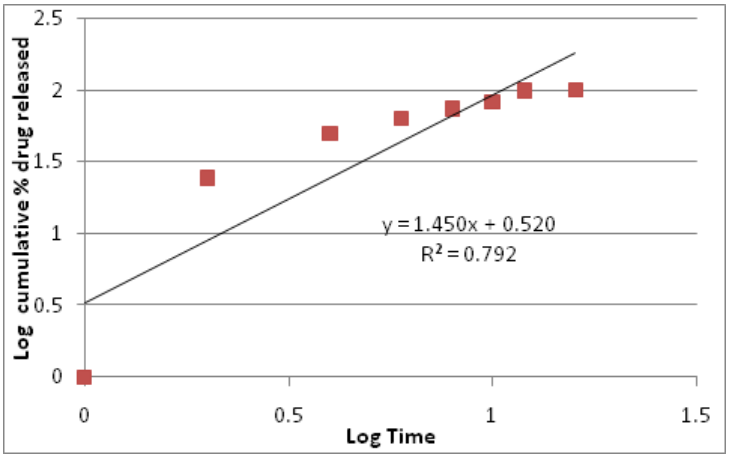

Figure 3: Korsmeyerpeppas

4. CONCLUSION

In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble drug was investigated using rivaroxaban as the model drug. Optimization of rivaroxaban liquisolid compacts was carried out using

Box– Behnken design by selecting liquid

load factor, amount of coating material and amount of magnesium oxide as independent variables and drug content and angle of repose as dependent variables. The results showed that solubility of water insoluble drug rivaroxaban was increased to greater extent thereby improving its dissolution rate. Thus liquisolid technology shall be used to improve the release rate of poorly water soluble drugs that will make the dosage form will be cost effective

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