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FORMULATION AND EVALUATION OF SOLID DISPERSION OF RIVAROXABAN CAPSULE

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ABSTRACT

The present study was aimed at preparing solid dispersion of Rivaroxabanto enhance its dissolution rate. Rivaroxaban is a poorly water soluble anti-diabetic drug which belongs to BCS class II drugs. Hence, it will be beneficial to increase its dissolution rate in order to improve its bioavailability by solid dispersion technique. The flow properties of the solid dispersions were influenced by physical, mechanical as well as environmental factors. The powder flowability can be determined by evaluating parameters such as the Bulk & Tapped densities, compressibility or Carr's index, Hauser's ratio and the Angle of repose. The bulk and tapped densities for solid dispersions powders were illustrated, the mean densities of liquid-solid powders were found to be from 0.318 to 0.389 g/cm^3 for bulk density and from 0.378 to 0.444 g/cm^3 for tapped density. Stability studies were carried out at 25˚C/60% RH, 30˚C/75% RH, 40˚C/75% RH for 3 months and there were no significant changes in physical and chemical properties of capsule of formulation F12 after 3 months. Based on the result F8 formulation was considered as the optimized formulation to design the solid dispersion by kneading method.

INTRODUCTION

The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. However, though popular, this route is not free from limitations of absorption and bioavailability in the milieu of gastrointestinal tract. Whenever a dosage form is administered orally, drug in the dosage form is released and dissolves in the surrounding gastrointestinal fluid to form a solution. This process is solubility limited. Once the drug is in the solution form, it passes across the membranes of the cells lining the gastro-Intestinal tract. This process is permeability limited. Then onwards the drug is absorbed into systemic circulation. In short, the oral absorption and hence bioavailability of drug is determined by the extent of drug solubility and permeability. [1]

A drug with poor bioavailability is the one with [2]

1. Poor aqueous solubility and slow dissolution rate in the biological fluids.
2. Poor stability of the dissolved drug at the physiological pH.
3. Inadequate partition coefficient and thus poor permeation through the biomembrane.
4. Extensive pre-systematic metabolism.

Three approaches in overcoming the bioavailability problems due to such causes are

1. The pharmaceutics approach which involves modification of formulation, manufacturing process, or the

physiochemical properties of the drug without changing the chemical structure.

2. The pharmacokinetic approaches in which the pharmacokinetics of the drug is altered by the modifying its chemical structure.

3. The biological approach whereby the route of the drug administration may be changed such as changing from oral to parental route.

The second approach of chemical modification has a number of drawbacks of being very expensive and time consuming, require repetition of clinical study and long time for regulatory aspects. Figure 1 illustrate the two rate determining steps (RDS) in the absorption of drugs from orally administered formulations

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou and Riegelman defined solid dispersions as "The dispersion of one or more active ingredients in an inert excipients or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states" [17]. Sekiguchi and Obi in 1961 first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug might also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug might be embedded in the matrix as amorphous materials [19].

Drug Profile

MATERIALS:

Rivaroxaban bulk drug was supplied as a gift sample from Mega-Fine Pharma Pvt Ltd. PEG 6000, PEG 20000, HPMC E15 were procured from S D Fine chem. Ltd. Mumbai ,HPC LH21, SOLUPLUS were procured from Colorcon, Mumbai and β-Cyclodextrin from Himedialaboratotypvt. Mumbai.

Determination of solubility

The solubility of Rivaroxaban in water, 0.1N HCL buffer, 6.8 Phosphate buffer, 4.5 Acetate buffer and six carriers tried to prepare the solid dispersions, namely, Polyethylene glycol 6000, Polyethylene glycol 20000, HPMC E15, HPC LH21, SOLUPLUS, β-Cyclodextrin were studied by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically. Specially, Rivaroxaban was mixed in 7ml screw capped vials with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were shaken on an automatic test tube shaking machine for 24 hours and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 Rpm for further settling of un-dissolved crystalline material and thereby obtaining a clear supernatant. After centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at 270 nm for their drug content. The results were extrapolated to determine the percent mg/ml of Rivaroxaban in its saturated solution with the solvents under investigation.

Melting point determination:

Melting point of the drug sample was determined by capillary method by using Melting point apparatus.

METHOD

Physical Method:

Te physical mixture were prepared using Rivaroxaban as drug and Polyethylene glycol 6000, Polyethylene glycol 20000, HPMC E15, HPC LH21, SOLUPLUS, β-Cyclodextrin as carriers in the ratio of 1:1 respectively.The required quantity of carriers was weighed in electronic digital balance, taken in a mortar and it was mixed with weighed quantity of drug wit geometric dilution method to form a homogenous physical mixture. The physical mixture was

dried properly using hot air oven at 45ºC for 1 hour. The dried mixture was passed through sieve no 80 and stored in desiccators for further study.

Kneading Method:

The kneading complexes were prepared using Rivaroxaban drug andPolyethylene glycol 6000, Polyethylene glycol 20000, HPMC E15, HPC LH21, SOLUPLUS, β-Cyclodextrin as carriers. The pure drug was considered as formulation F0. The required quantity of carriers was weighed in electronic balance, taken in a mortar and it was dissolved in Isopropyl alcohol by using pestle. Accurately weighed quantity of drug was then added to isopropyl alcohol solution of carrier. The dispersion was then continuously stirred to form a paste was prepared. Above paste thus prepared was kneaded properly and kneaded complex was dried properly using hot air oven at 45ºC for 1Hour. Then dried kneaded complex was passed through sieve no 80 and stored in desiccators for further study.Composition of each ingredient is shown in table 1.

Encapsulation:

The prepared solid dispersion were mixed with lactose, magnesium Stearate and Aerosil and filled into capsules.

EVALUATION OF POWDER BLEND:

Determination of bulk density & tapped density:

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987).

The bulk density and the tapped density were calculated using the following formulae:

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

Compressibility Index (Carr's index): Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. The less compressible material is the more flowable. (Lachman et al., 1987).

$$CI = (TD-BD) \times 100/TD$$

Where, TD is the tapped density and BD is the bulk density.

Hausner's Ratio: It is the ratio of tapped density and bulk density. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Angle of repose: The angle of repose of powder blend was determined by the funnel method. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation:

$$\theta = \tan^{-1} h/r$$

Where, h and r are the height and radius of the powder cone.

Compatibility studies: IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6tons pressure .It was scanned from 4000 to 400 cm-1 in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks.

EVALUATION OF CAPSULES:

Drug content estimation: Weigh and powder 20 capsules. Weigh accurately a quantity of powder containing equivalent weight of 5 capsules weight of Rivaroxaban into a 100 ml volumetric flask. Dissolve with the aid of small quantities of methanol, make up to 100 ml with methanol and filter. Dilute 10 ml of filtrate to 100 ml with 4.5 Acetate buffer and mix. Pipette out 10 ml of solution into a 100 ml volumetric flask and make up to 100 ml with 7.2 phosphate buffer and mix. Measure the absorbance of the

resulting solution at 270nm in UV. Results are shown in Table no (15).

In-vitro drug release studies: In vitro drug release of the samples was carried out using USP-type I dissolution apparatus (Basket type). The dissolution mediums, used was 4.5 Acetate buffer 900ml (as specified by the office of generic drugs USFDA), placed into the dissolution flask maintaining the temperature of 37±0.5°C. Rivaroxabancapsule were placed in each flask of dissolution apparatus. The apparatus was allowed to run for 1 hour at 50 RPM. Samples measuring 10ml were withdrawn at specified time intervals. The samples were filtered and analyzed at 270 nm. The cumulative percentage drug release was calculated.

Release kinetics: The results of *in vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus time. (Zero order kinetic model)

Zero-Order Kinetics:

A zero-order release would be predicted by the following equation.

$$\mathbf{At = A_o - K_o t}$$

Where, At = Drug release at time t

A_o = Initial drug concentration

K_o = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to k_o..

First-Order Kinetics:

A first order release would be predicted by the following equation.

$$\mathbf{Log\ C = Log\ Co - K_t / 2.303}$$

Where, C = Amount of drug remained at time t

C_o = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

Stability Studies:

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated.

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing:

1. 25˚C/60% RH analyzed every month for period of three months.
2. 30˚C/75% RH analyzed every month for period of three months.
3. 40˚C/75% RH analyzed every month for period of three months.

RESULT & DISCUSSION:

Evaluation of flowability and compressibility of solid dispersion powders:

Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. The flow properties of the solid dispersions were influenced by physical, mechanical as well as environmental factors. The powder flowability can be determined by evaluating parameters such as the Bulk & Tapped densities, compressibility or Carr's index, Hausner's ratio and the Angle of repose.

The results obtained for evaluation of compressibility index and Hausner's ratio is in Table 2

Compatibility studies:

The spectrum obtained after the analysis is shown in Fig 4-11. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Rivaroxaban pure drug were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

	Ingredients	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Rivaroxaban	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20 mg	20mg	20mg	20mg	20mg
2	PEG6000	30mg	30mg	-	-	-	-	-	-	-	-	-	-
3	PEG20000	-	-	30mg	30mg	-	-	-	-	-	-	-	-
4	HPMC E15	-	-	-	-	30mg	30mg	-	-	-	-	-	-
5	Soluplus	-	-	-	-	-	-	30mg	30 mg	-	-	-	-
6	B-Cyclodextrin	-	-	-	-	-	-	-	-	30mg	30mg	-	-
7	HPC L21	-	-	-	-	-	-	-	-	-	-	30mg	30mg
8	Lactose	38mg	38mg	38mg	38mg	38mg	38mg	38mg	38 mg	38mg	38mg	38mg	38mg
9	Aerosil	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
10	Mg Sterate	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg	1mg
11	Iso Propyl Alcohol	-	0.2ml	-	0.2ml	-	0.2ml	-	0.2 ml	-	0.2ml	-	0.2ml
12	Wt of Ingredients	100	100	100	100	100	100	100	100	100	100	100	100
13	Method of Preparation	Physical Method	Kneading Method	Physical Method	Kneading Method	Physical Method	Kneading Method	Physical Method	Kneading Method	Physical Method	Kneading Method	Physical Method	Kneading Method
14	Mfg Process	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule	Capsule

Table 1. Formulation of solid dispersion

Formulation	Bulk density	Tapped density	Carr's Index	Hausner's Ratio	Angle of Repose
Prepared Conventional	0.371	0.457	18.81	1.231	28.86
F1	0.318	0.389	18.25	1.223	24.93
F2	0.331	0.399	17.04	1.205	24.25
F3	0.329	0.396	16.91	1.203	25.05
F4	0.345	0.409	15.64	1.185	26.40
F5	0.356	0.411	13.38	1.154	25.79
F6	0.389	0.444	12.38	1.141	27.56
F7	0.362	0.410	11.70	1.132	27.66
F8	0.338	0.378	10.58	1.118	28.67
F9	0.337	0.403	16.31	1.195	25.06

F10	0.350	0.414	15.45	1.182	26.71
F11	0.343	0.402	14.67	1.172	26.94
F12	0.367	0.422	13.03	1.149	27.10

Table 2: Pre-compression Studies

Formulation	Bulk density	Tapped density	Carr's Index	Hausner's Ratio	Angle of Repose
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F2	0.331	0.399	17.04	1.205	24.25
F3	0.329	0.396	16.91	1.203	25.05
F4	0.345	0.409	15.64	1.185	26.40
F5	0.356	0.411	13.38	1.154	25.79
F6	0.389	0.444	12.38	1.141	27.56
F7	0.362	0.410	11.70	1.132	27.66
F8	0.338	0.378	10.58	1.118	28.67
F9	0.337	0.403	16.31	1.195	25.06
F10	0.350	0.414	15.45	1.182	26.71
F11	0.343	0.402	14.67	1.172	26.94
F12	0.367	0.422	13.03	1.149	27.10

Table 2: Pre-compression Studies

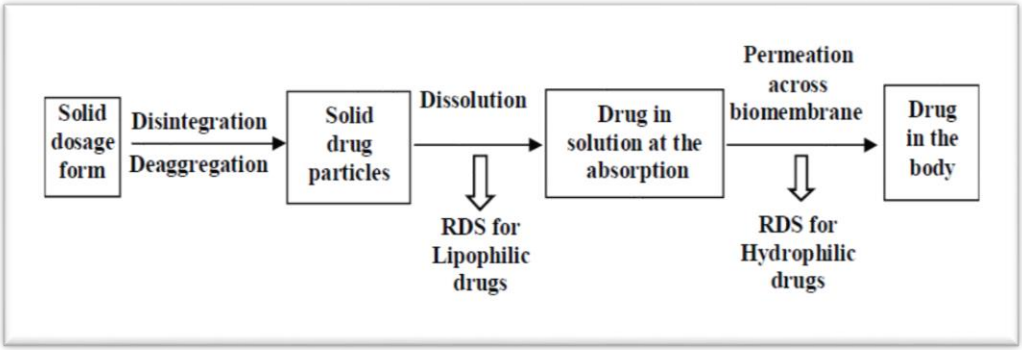


Figure 1: Two rate determining steps (RDS) in the absorption of drugs from orally administered formulations

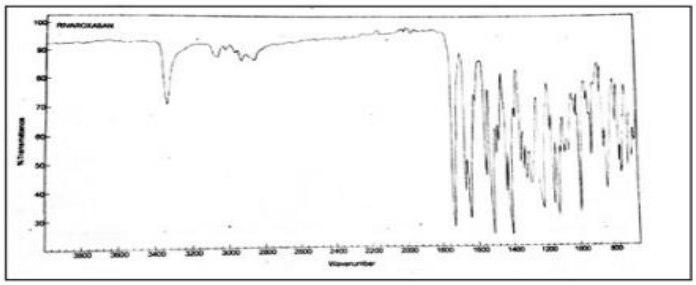


Figure 2: FTIR Spectra of Pure Drug Rivaroxaban

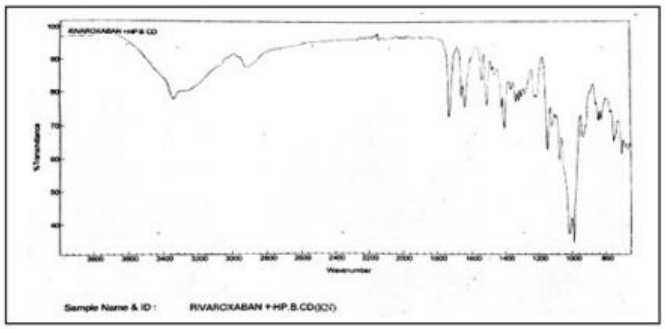


Figure 3: FTIR Spectra of Physical Mixture of Rivaroxaban

Formulation	Drug content (%)
F1	95.69
F2	94.67
F3	96.19
F4	93.67
F5	93.15
F6	94.17
F7	95.18
F8	98.73
F9	96.20
F10	96.70
F11	93.16
F12	97.21

Table 3: Drug Content

Sr.no	**%drug release-pH4.5 acetate buffer**											
	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	**5min**	46.3	43.5	44.3	36.8	24.4	22.6	48.0	73.0	33.7	28.4	36.4	52.1
2	**10min**	62.0	64.1	62.2	63.2	32.4	30.6	57.8	84.0	42.7	34.9	71.3	74.2
3	**15min**	64.6	67.5	71.3	68.3	39.2	38.5	63.8	91.1	53.1	49.3	78.6	78.2
4	**30min**	70.0	73.5	75.1	71.5	52.6	49.0	85.1	95.7	72.8	63.7	87.7	88.4
5	**45min**	72.9	76.0	79.1	76.5	53.5	52.5	98.1	97.8	86.6	77.5	98.3	92.2
6	**60min**	82.2	85.2	89.7	89.0	61.1	58.3	99.7	99.6	98.1	94.4	99.5	98.8

Table 4: Dissolution profile of solid dispersions in pH 4.5 buffer:

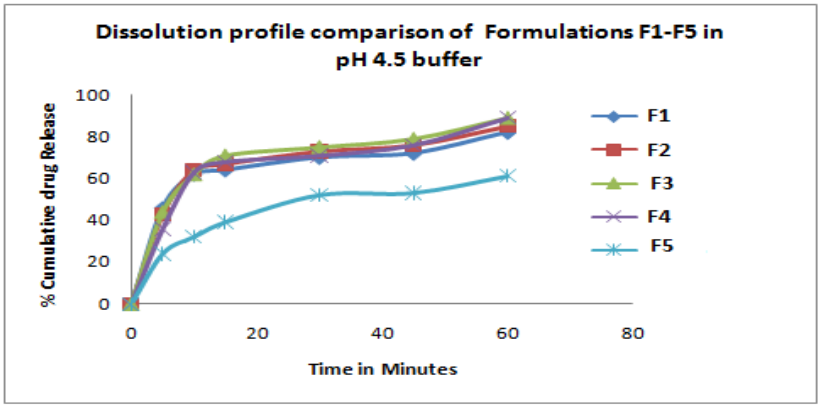


Figure 4: Dissolution profile comparison of Formulations F1-F5 in pH 4.5 buffer

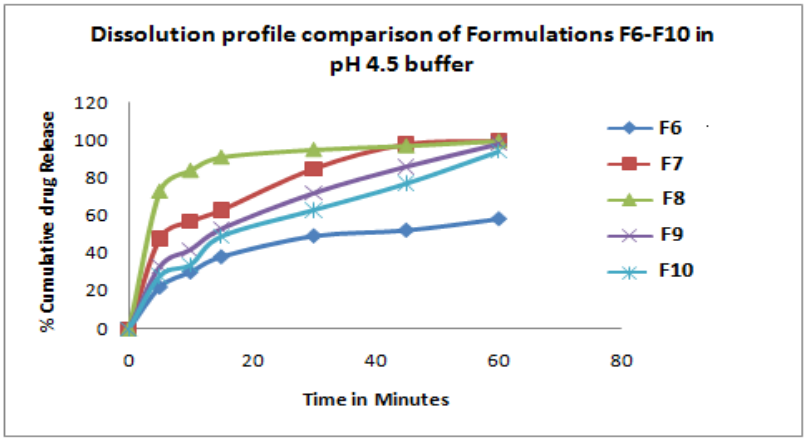
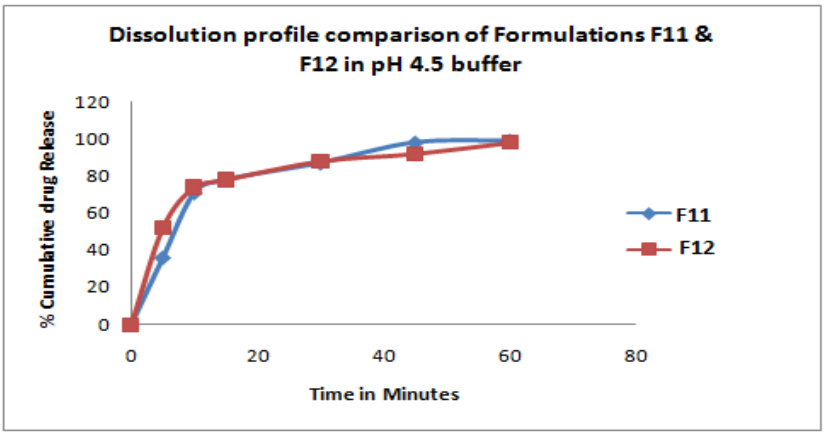


Figure 5: Dissolution profile comparison of Formulations F6-F10 in pH 4.5 buffer



Release kinetics	**R^2**	**Intercept**	**Slope**
Zero order	0.412	-4.568	1.011
First order	0.903	53.15	1.626

Table 5: kinetic studies of solid dispersion

Zero Order:

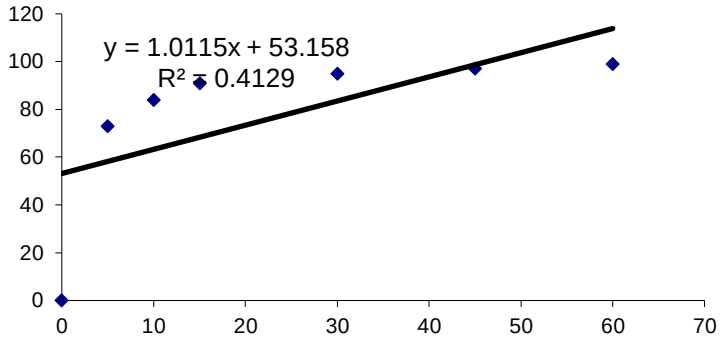


Figure 7: Release profile of Rivaroxaban solid dispersion according to Zero Order

First Order:

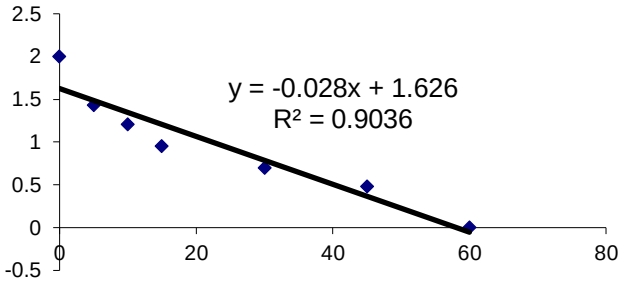


Figure 8: Release profile of Rivaroxaban solid dispersion according to First Order

Formulation code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per specifications
F8	25˚C/60%RH % Release	97.11	96.87	96.66	96.64	NLT 85%
F8	30˚C/75%RH % Release	97.05	96.89	96.88	96.41	NLT 85%
F8	40˚C/75%RH % Release	97.11	96.92	96.63	96.62	NLT 85%
F8	25˚C/60%RH Assay value	97.72	96.70	96.19	95.69	NLT 90% NMT 110%
F8	30˚C/75%RH Assay value	97.72	97.71	96.20	95.69	NLT 90% NMT 110%
F8	40˚C/75%RH Assay value	97.21	97.20	96.70	96.19	NLT 90% NMT 110%

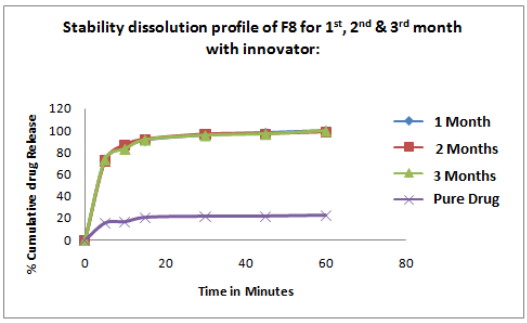


Figure 9: Stability Dissolution Profile of F8 for 1st, 2nd& 3rd months with Innovator

Table 6: Results of stability studies of optimized formulation F8:

Sr.No	Time (in minutes)	Innovator	F8 1st Month	F8 2nd Month	F8 3rd Month
1	0	0	0	0	0
2	5	15.448	73.12	72.46	73.69
3	10	16.588	84.23	86.95	83.26
4	15	20.481	91.34	92.03	91.57
5	30	21.526	95.82	96.52	95.59
6	45	21.621	97.79	97.12	96.85
7	60	22.38	99.67	98.66	99.64

Table 7: Stability dissolution profile of F8 for 1st, 2nd& 3rd month

Evaluation of post compression parameters:

Drug content estimation: F8 showing maximum drug content and F5 shows least content. Results showed in table no (15).It was clear from Table (15) that all the investigated solid dispersion capsules complied with the Pharmacopoeial requirements with regard to their content uniformity, which was found to lie within the range of 93.15% to 98.73%.

***IN VITRO* DISSOLUTION STUDY:**

The dissolution study for all the 12 formulations was carried out in pH 4.5 Acetate buffer. Fig 12-18 shows the dissolution profile of 12 formulations and conventional capsule of pure drug. Solid dispersions displayed more distinct in-vitro in two different methods i.e., physical method and kneading method by using various solubility enhancing polymers like PEG6000,PEG20000,HPMC E15,HPC LH21,β-Cyclodextrin &Soluplus.

The prepared solid dispersions where performed for dissolution studies in pH 4.5 acetate buffer.

From the above results it has been concluded that formulations prepared with Soluplus has greater dissolution rate followed by PEG 20000 and other polymers based upon the respective saturation solubility studies.

RELEASE KINETICS:

In vitro release data obtained for the formulation F8 are shown in table no 23: shows release kinetics of Rivaroxaban compacts. The cumulative percentage drug release data obtained were fitted to Zero order, first order. (Fig no: 21 to 24). The slopes and the regression coefficient of determinations (r^2) were listed in table no: release characteristics than the conventional drug. Among all, F8 showed higher release rate (99.645% at the end of the 60th minute. Pure drug showed only 22.38% cumulative release

Dissolution conditions:

Apparatus: I

Dissolution Medium: (4.5 Acetate buffer)

Volume: 900 ml, Rpm: 50

Temperature: 37 ± 5˚C, λ_{max}: 270 nm

Figure 6: Dissolution profile comparison of Formulations F11 & F12 in pH 4.5 buffer

For the pure drug the % release was found to be very less due to its poor solubility characteristic nature. Hence in order to improve the solubility nature, the drug was formulated as solid dispersions

24. The coefficient of determination indicated that the release data was best fitted with first order kinetics.

STABILITY STUDIES: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Here the capsules were loaded at accelerated conditions at 25°C/ 60% RH, 30° C/ 75% RH, 40°C/ 75% RH in a stability chamber. Samples were withdrawn at initial, 30, 60 and 90 days and evaluated for drug content and dissolution time. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

CONCLUSION

Solubility is the major criteria to achieve the desired concentration of the drug in the systemic circulation. About 80% of the drugs are poorly soluble. To overcome such a problem, several techniques have been developed to enhance the solubility of those drugs. Among them, solid dispersion is one of the most promising and new technique which promotes the dissolution rate of water-insoluble drugs. For the pure drug, the percentage of drug release was found to be very less due to its poor solubility characteristic nature. Hence in order to improve the solubility nature, the drug was formulated as solid dispersions in two different methods i.e., physical method and kneading method by using various solubility enhancing polymers like PEG6000, PEG20000, HPMC E15, HPC LH21,β-CYCLODEXTRIN &, SOLUPLUS. It was clear that all the investigated solid dispersion capsules complied with the Pharmacopoeial requirements concerning their content uniformity, which was found to lie within the range of 93.15% to 98.73%. Based on mathematical data revealed from models, it was concluded that the release data were best fitted with First-order kinetics. Stability studies showed that there were no significant changes in the physical and chemical properties of a formulation F8 after 3 months.

This research work has produced encouraging results in terms of increasing the *in vitro* dissolution of poorly soluble drugs such as Rivaroxaban using solid dispersion technology and we expect a good correlation between the *in vitro* and *in vivo* performance of the formulations.

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