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Research Article

Enhancement of Dissolution of Rivaroxaban Using Complexation with ß-cyclodextrins

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A B S T R A C T

The solubilization of poorly soluble drugs belonging to Class II of the Biopharmaceutical Classification System (BCS) is often a challenge in screening studies of new chemical substances as well as in formulation design and development. One of the most difficult aspects of formulation design is the Solubility properties. A number of methods can be used to improve the solubilization of poorly water-soluble drugs and further improve their bioavailability. Rivaroxaban, an anticoagulant, is classified as a poorly soluble BCS class II drug. Solid dispersion technologies provide promising results for improving the oral absorption and bioavailability of BCS class II drugs. The present study highlights the critical role of particle size reduction and increased surface area in improving the solubility, dissolution rate and subsequent bioavailability of rivaroxaban. The purpose of this study was to investigate the efficacy of hydrophilic polymers in a inclusion complex and solid dispersion formulation in improving the solubility and dissolution rate of rivaroxaban (RXB), a poorly soluble drug. The solubility studies of drug β-CD systems in water at 25°C revealed that the solubility of drug increased linearly for the preparation of complexes by kneading method.

Key words: Rivaroxaban, ß cyclodextrin, solubility, dissolution rate

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INTRODUCTION

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. Low solubility is the up hilled task for the researchers and scientists [1]. The Biopharmaceutics Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Solubility is a major challenge for formulation scientist [2-3]. Any drug to be absorbed must be present in the form of solution at the site of absorption. Different solubility enhancement techniques like solid dispersion, solvent deposition, micronization etc. have been employed for rectification of solubility issue in pharma industry. Amongst these; Inclusion complexation is a classical way to ameliorate the solubility of a drug with natural cyclodextrins. Cyclodextrins (CDs) are formed in the result of bacterial degradation of cellulose. These are amphiphilic product

(cyclic oligosaccharides) which consist of (α-1,4) linked α-D-glucopyranose units with lipophilic central cavity and a hydrophilic outer surface area [4-5]. Cyclodextrin inclusion complexation may be a potential approach to ameliorate the saturated solubility, dissolution profile and ultimately the bioavailability of the BCS class II drugs; and class IV drugs in some cases. Cyclodextrins are a group of oligosaccharides tend to capture the hydrophobic moiety into their cavity and develop host-guest relationship. Their outer surface is hydrophilic due to the presence of hydroxyl groups while the inner cavity is hydrophobic due to the restricted number of water molecules. Their solubilization efficiency is also enhanced in the presence of different hydrophilic polymers [6-7]. Rivaroxaban is an anticoagulant, factor of Xa inhibitor. Rivaroxaban is commercially available as tablets. With its dose for treating deep vein thrombosis (DVT) is 10 mg once daily. Rivaroxaban has been shown to be 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 low water solubility and belongs to BCS Class II drug. Hence it has planned to enhance the solubility of drug and, thereby dissolution rate of formulation, which may enhance the bioavailability of the drug. Rivaroxaban competitively inhibits free and clot-bound factor Xa. Factor Xa is needed to activate prothrombin (factor II) to thrombin (factor II a). Thrombin is a serine protease that is required to activate fibrinogen to fibrin, which is the loose meshwork that completes the clotting process. Since one molecule of factor Xa can generate more than 1000 molecules of thrombin, selective inhibitors of factor Xa are profoundly useful in terminating the amplification of thrombin generation [8-10]. The aim of present investigation is to enhance the solubility of poorly soluble drug rivaroxaban by appropriate solubility enhancement method and formulate the tablets dosage form.

MATERIALS AND METHODS

Materials: A gift sample of rivaroxaban was received from Alkem Laboratories (Mumbai, India). β-cyclodextrins was obtained from Sigma Aldrich.All other solvents and ingredients used were of analytical grade.

METHODS

Preparation of Inclusion Complex by Kneading method: The inclusion complex of rivaroxaban and β -cyclodextrins was prepared by the kneading method. In which distilled water was used to prepare drug: carrier complex in a mortar by grinding ingredients for half an hour. After grinding, the wet was mass left to air dry at room temperature for 48 hours with intermittent mixing and agitation. The complexes were made in different ratios with respect to drugs and carriers [11].

Table 1: Composition of inclusion complex of rivaroxaban by kneading method

F. Code	Drug	Carrier	Drug : Carrier Ratio
RKM1	Rivaroxaban	ß-cyclodextrins	10 : 90
RKM2	Rivaroxaban	ß-cyclodextrins	20 : 80
RKM3	Rivaroxaban	ß-cyclodextrins	30 : 70
RKM4	Rivaroxaban	ß-cyclodextrins	40 : 60
RKM5	Rivaroxaban	ß-cyclodextrins	50 : 50

Preparation of solid dispersion by solvent evaporation method: A blend of lactose and MCC in given ratio was mixed with the solution of rivaroxaban in chloroform (2mL). The solvent was allowed to evaporate at room temperature with substantially stirring. The solid wet mass was passed through a #40 mesh sieve; upto granules were prepared and subsequently dried at 60°C using a vacuum until a constant weight was obtained for enhancement of solubility at the simulated gastric fluid pH1.2 buffer. The granules were filled into 0-size hard gelatine capsules by own hand manually [12].

Table 2: Composition of solid dispersion of rivaroxaban by solvent evaporation method

F. Code	Drug	Lactose (mg)	Microcrystalline cellulose (mg)	Solvent Chloroform(ml)
RSDSE1	Rivaroxaban (20mg)	10	70	2
RSDSE2	Rivaroxaban (20mg)	20	60	2
RSDSE3	Rivaroxaban (20mg)	30	50	2
RSDSE4	Rivaroxaban (20mg)	40	40	2
RSDSE5	Rivaroxaban (20mg)	30	50	2

Preparation of inclusion complex by solvent co-evaporation method: Rivaroxaban and β-CD were dissolved in ethanol : distilled water ratio (100 ml), respectively. Then, these solutions were mixed in a flask and stirred at 600 rpm for 2 h at 50 °C. The obtained clear solution was evaporated at 45 °C using a rotary evaporator (BÜCHI, rotavapor R-215) rolling at 100 rpm. The solid residue was further dried at 50 °C for 24 h and stored in bottles and kept in the refrigerator.

Table 3: Composition of inclusion complex of rivaroxaban by solvent co-evaporation method

F. Code	Drug	Carrier	Drug : Carrier Ratio	Solvent (5 ml)
RSE1	Rivaroxaban	ß-cyclodextrins	10 : 90	Ethanol : Water (1:1)
RSE2	Rivaroxaban	ß-cyclodextrins	20 : 80	Ethanol : Water (1:1)
RSE3	Rivaroxaban	ß-cyclodextrins	30 : 70	Ethanol : Water (1:1)
RSE4	Rivaroxaban	ß-cyclodextrins	40 : 60	Ethanol : Water (1:1)
RSE5	Rivaroxaban	ß-cyclodextrins	50 : 50	Ethanol : Water (1:1)

Preparation of solid dispersion by co-grinding method: The SD was prepared by cogrinding dispersion process as mixture of solvent system was available on previous process solvent evaporation method. The influence of addition of solubilizing agents i.e. PVP, PEG 400, or PG over drug solubility at the simulated gastric fluid pH1.2 buffer with more dissolution profile was discussed. The dissolution medium solution (1 mL) of PVP, PEG 400, or PG was triturated with drug (20 mg) until a creamy homogeneous were obtained. The prepared drug solvent polymer mixture was further triturated with excipients lactose and MCC for 10 min. The solid wet mass was passed through a #40 mesh sieve, and subsequently dried at 60°C using a vacuum until a constant weight was obtained. The granules were filled into 0-size hard gelatine capsules by own hand manually. The formulations were prepared by using the variability in polymeric concentration of PEG 400, PG, and PVP K30 as independent variables. Tween 80 (10 mg) and SLS (10 mg) were dissolved in the aqueous solution of solubilizing agents.

Table 4: Composition of solid dispersion of rivaroxaban by co-grinding method

S. No.	F. Code	Polyethylene glycol (PEG) 400 (mg)	Propylene glycol (PG) (mg)	Polyvinylpyrrolidone (PVP) K30 (mg)
1	RSDCG1	20	20	20
2	RSDCG2	20	10	30
3	RSDCG3	20	30	10
4	RSDCG4	10	20	30
5	RSDCG5	30	20	10

Characterization of drug complexes and solid dispersion:

Organoleptic properties: The organoleptic properties of Rivaroxaban such as color, odor and taste were noted by sensory organs**.**

Physical Characteristics:

Density: The drug complex & solid dispersion was exactly weighed and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined.

Particle size: The average particle size (d_{avg}) of drug complex was determined by using a microscope (66172/Olympus, 100 X, Olympus Pvt. Ltd., New Delhi) fitted with ocular micrometer and stage micrometer.

Flow properties: The flow properties of drug complex were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (ɵ). The Carr's index ((I_C)) and Hausner's ratio (H_R) of drug powders were calculating according to previous discuss equations.

Solubility determination: The solubility of drug complex was determined in various dissolution media (Water, 0.1 N HCl, pH 7.4 phosphate buffer and pH 6.8 phosphate buffer was discussed in earlier. The solubility value of drug in different medium was determined by UV spectrophotometric method described in earlier. The samples were filtered by using Whatmann filter paper (0.45µm pore size). The solubility assessment of drug was determined by UV spectrophotometric method at 249 nm of rivaroxaban [13].

Wettability study: The various formulations i.e. physical mixture complexes or solid dispersion (1 g) was placed in a sintered glass funnel (55 mm i.d.). The funnel was plunged into beaker containing water so that the surface of the water in the beaker remained at the same level as the powder in the funnel. Methylene blue powder (100 mg) was poured onto the surface of the test sample. The time required for wetting the methylene blue powder was measured.

Percent (%) Drug content: The various formulations i.e. physical mixture complexes or solid dispersion (1 g) were taken randomly and crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCl and filtered. This solution was analyzed in UV spectrophotometer at λmax 249 nm of rivaroxaban.

In vitro Dissolution study: In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.50C with 50 rotations per minute. 1ml of aliquots was withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug

content at λ max 262 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported [14-15].

Drug release kinetic study: Mechanism of drug from was investigated by various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. Drug dissolution behaviors depend on the value of correlation coefficient (r2).

RESULTS AND DISCUSSION:

The organoleptic properties of rivaroxaban complexes such as color, odor and taste were noted by sensory organs**.** The properties was pale yellow, odorless to bitter in taste. Bulk densities of drug complexes, SD were found from 0.292 gm/cm^3 to 0.296 gm/ cm^3 and tapped densities of drug complexes, SD were found 0.311 gm/cm^3 to 0.316 gm/cm^3. The particle size of drug complex powder and SD were found 105 µm to 112 µm. The flow properties of drug complex were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (ɵ). The drug complex with kneading method exhibited excellent flow, whereas other drug complexes exhibited good flow characteristics. The formulation SD i.e. solid dispersion method showing excellent flow due to having good particle size than formulations with kneading method (Table 1).

Table 5: Physical characterization of rivaroxaban formulations

F. Code	Properties			Density (gm/ cm^3)		Particle size (µm)	Flow Properties		
	Color	Odor	Taste	lk density	Tapped density		Carr's index (%)	Hausner's ratio	Angle of repose (θ)
RKM1	Pale Yellow	Odorless	Bitter	0.293	0.313	112	12.41±0.011	1.10±0.04	23.1±0.012
RKM2	Pale Yellow	Odorless	Bitter	0.296	0.316	108	13.71±0.011	1.12±0.01	24.7±0.011
RKM3	Pale Yellow	Odorless	Bitter	0.295	0.315	107	13.89±0.011	1.13±0.03	25.2±0.013
RKM4	Pale Yellow	Odorless	Bitter	0.294	0.314	105	13.11±0.012	1.12±0.04	24.1±0.012
RKM5	Pale Yellow	Odorless	Bitter	0.293	0.312	109	12.41±0.011	1.10±0.04	23.1±0.012
RSDSE1	White Yellow	Odorless	Bitter	0.293	0.313	110	12.12±0.012	1.15±0.03	20.02±0.09
RSDSE2	White Yellow	Odorless	Bitter	0.296	0.316	109	12.15±0.013	1.17±0.01	21.12±0.12
RSDSE3	White Yellow	Odorless	Bitter	0.292	0.311	112	12.10±0.011	1.16±0.02	20.11±0.10
RSDSE4	White Yellow	Odorless	Bitter	0.295	0.312	108	12.09±0.011	1.15±0.01	19.12±0.03
RSDSE5	White Yellow	Odorless	Bitter	0.294	0.315	106	11.09±0.09	1.14±0.11	19.02±0.01

Table 6: Physical characterization of rivaroxaban formulations

F. Code	Solubility (mg/ml)				Wetting time (Min.)	Drug content (%.)
	Water	0.1 N HCl	Phosphate buffer pH 6.8	Phosphate buffer pH 7.4		
RKM1	17.231±1.21	15.111±1.02	14.024±1.11	13.012±1.11	5.19	98.87
RKM2	18.121±1.11	15.241±1.01	14.032±1.12	13.131±1.22	5.22	99.08
RKM3	18.121±1.11	15.182±1.12	14.125±1.10	13.241±1.32	5.29	99.04
RKM4	19.221±1.12	15.141±1.13	14.233±1.12	13.031±1.23	5.43	98.98
RKM5	18.211±1.11	15.241±1.22	14.314±1.12	13.124±1.17	5.11	98.77
RSDSE1	17.101±1.21	12.982±1.01	12.711±1.18	13.111±1.12	5.15	97.67
RSDSE2	18.103±1.11	12.123±1.11	12.722±1.21	13.213±1.11	5.54	97.88
RSDSE3	18.102±1.12	12.211±1.21	12.732±1.23	13.161±1.02	5.32	97.74
RSDSE4	18.111±1.14	12.112±1.21	12.341±1.22	13.321±1.11	5.71	97.88
RSDSE5	18.113±1.11	12.311±1.13	12.261±1.21	13.241±1.01	5.18	97.57

Table 7: Physical characterization of rivaroxaban formulations

F. Code	Properties			Density (gm/ cm^3)		Particle size (µm)	Flow properties		
	Color	Odor	Taste	Bulk density	Tapped density		Carr's index (%)	Hausner's ratio	Angle of repose (θ)
RSE1	White Yellow	Odorless	Bitter	0.293	0.313	110	12.21±0.013	1.17±0.01	23.14±0.004
RSE2	White Yellow	Odorless	Bitter	0.296	0.316	108	12.11±0.011	1.12±0.01	22.18±0.008
RSE3	White Yellow	Odorless	Bitter	0.294	0.314	107	12.21±0.013	1.15±0.02	23.16±0.009
RSE4	White Yellow	Odorless	Bitter	0.298	0.317	102	12.08±0.008	1.08±0.01	21.17±0.012
RSE5	White Yellow	Odorless	Bitter	0.292	0.314	109	12.14±0.009	1.06±0.02	22.08±0.008
RSDCG1	White to pale Yellow	Odorus	Slight bitter	0.292	0.311	110	12.22±0.011	1.18±0.01	23.19±0.007
RSDCG2	White to pale Yellow	Odorus	Slight bitter	0.296	0.316	109	12.17±0.008	1.12±0.01	22.16±0.009
RSDCG3	White to pale Yellow	Odorus	Slight bitter	0.292	0.312	112	12.18±0.013	1.16±0.01	21.22±0.012
RSDCG4	White to pale Yellow	Odorus	Slight bitter	0.295	0.316	109	12.08±0.09	1.07±0.02	22.27±0.013
RSDCG5	White to pale Yellow	Odorus	Slight bitter	0.294	0.314	111	12.22±0.011	1.18±0.01	23.19±0.007

Table 8: Physical characterization of rivaroxaban formulations

F. Code	Solubility (mg/ml)				Wetting time (Min.)	Drug content (%.)
	Water	0.1 N HCl	Phosphate buffer pH 6.8	Phosphate buffer pH 7.4		
RSE1	17.081±1.04	3.142±0.81	2.011±1.31	2.726±1.85	6.28	95.45
RSE2	18.012±1.01	3.784±0.92	2.111±1.21	2.834±1.82	6.02	95.66
RSE3	18.012±1.07	3.843±0.43	2.231±1.17	2.822±1.613	6.14	95.52
RSE4	17.712±1.06	3.544±0.48	2.512±1.13	2.916±1.26	6.05	95.4
RSE5	16.988±1.07	3.745±0.99	2.741±1.16	2.822±1.25	6.21	95.35
RSDCG1	21.119±1.01	2.999±1.31	2.981±1.21	3.321±1.03	5.47	99.78
RSDCG2	17.116±1.21	2.622±1.23	2.671±1.12	3.211±1.23	5.41	99.84
RSDCG3	18.118±1.11	2.712±1.31	2.761±1.23	3.111±1.09	5.37	99.67
RSDCG4	17.117±1.04	2.342±1.31	2.799±1.21	3.241±1.16	5.26	99.98
RSDCG5	21.119±1.01	2.999±1.31	2.981±1.21	3.321±1.03	5.34	99.57

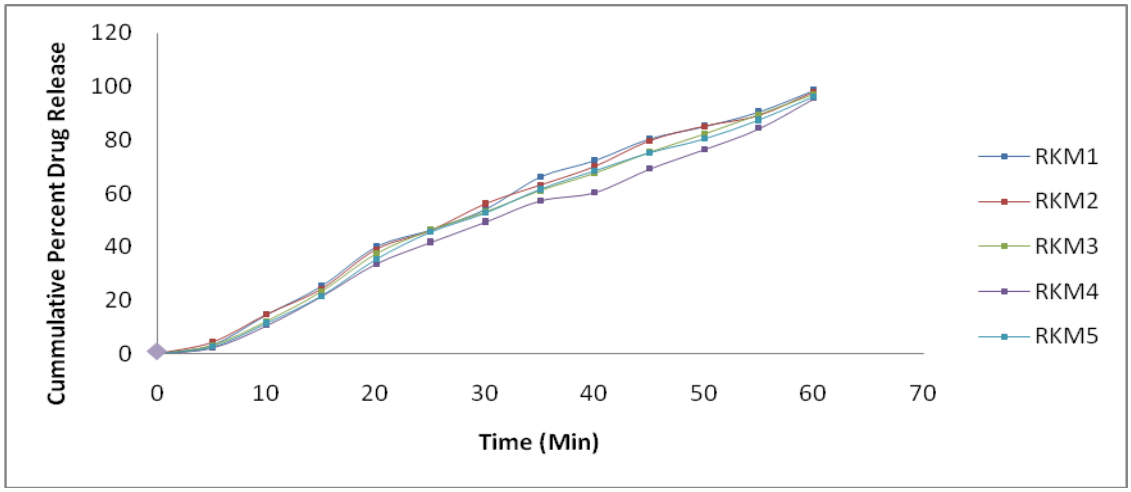

Figure 1: In-Vitro Drug Release Profile of Inclusion Complex of Rivaroxaban by Kneading Method

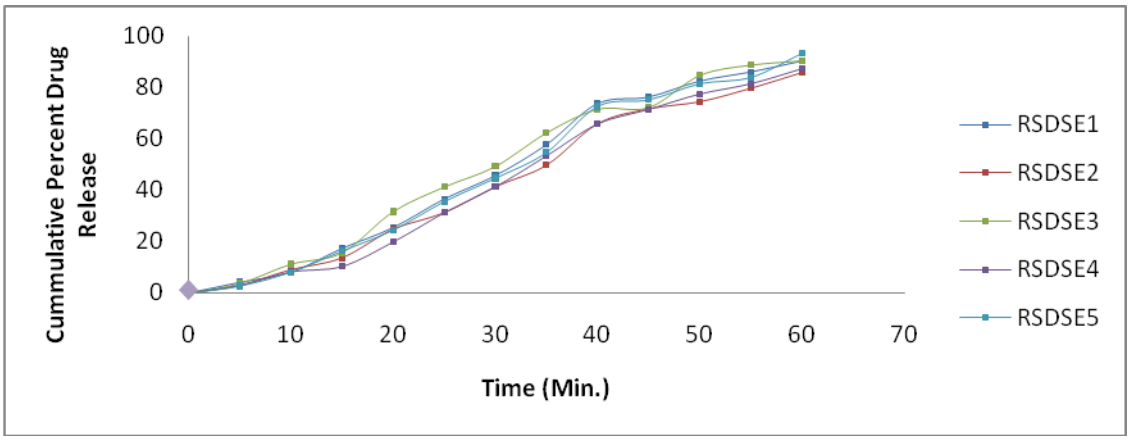

Figure 2: In-Vitro Drug Release Profile of Solid Dispersion of Rivaroxaban by Solvent Evaporation Method

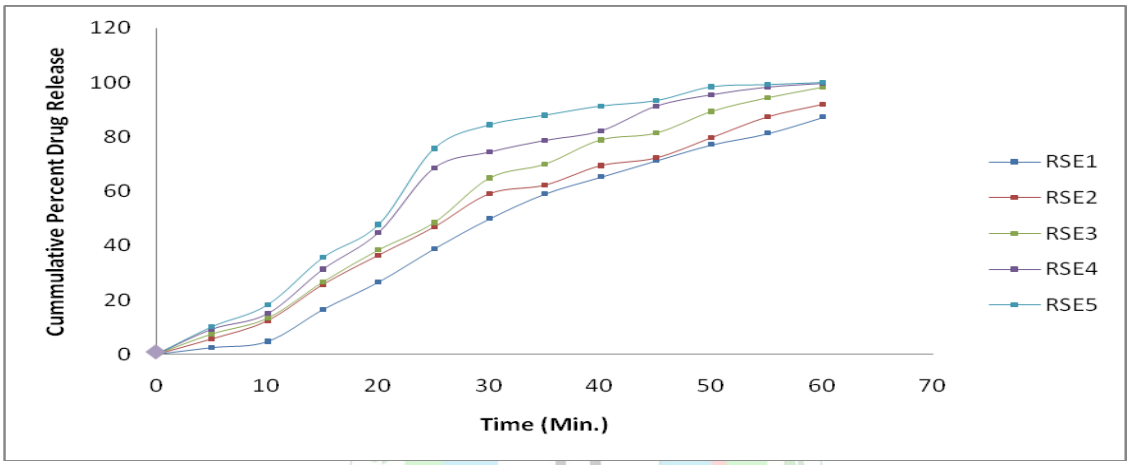

Figure 3: In-Vitro Drug Release Profile of Inclusion Complex of Rivaroxaban by Solvent Co-Evaporation Method

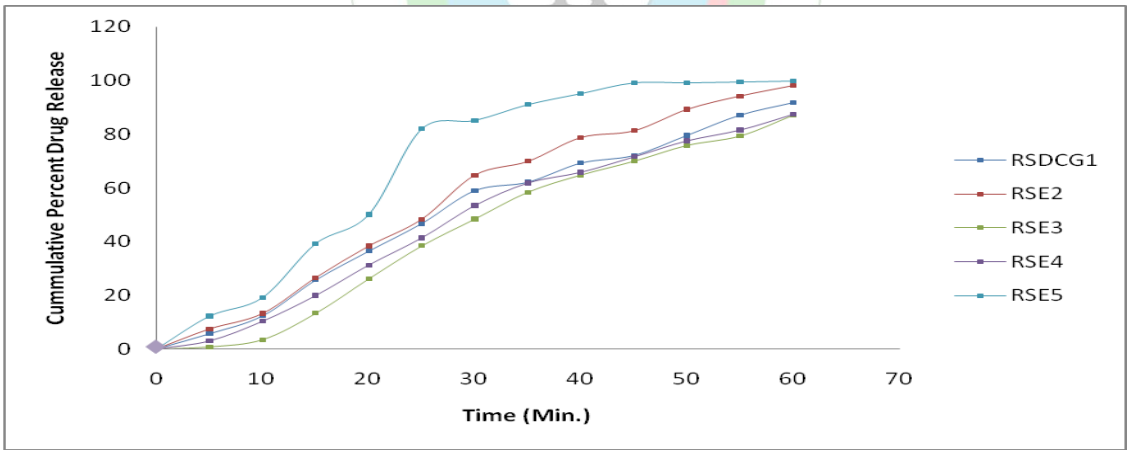

Figure4: In-Vitro Drug Release Profile of Solid Dispersion of Rivaroxaban by Co-Grinding Method

The solubility studies of drug β-CD systems in water at 25°C revealed that the solubility of drug increased linearly for the preparation of complexes by kneading method. Solid inclusion complexes of drug were prepared by kneading method appeared that the solubility behaviour of the material was modified by altering its surrounding environment. The solubility of physical mixtures and solid complexes prepared with a number of methods increased due to the surface tension lowering effect of the β-cyclodextrin, resulting in wetting of hydrophobic drug surface. The increase in solubility was also due to the formation of water-soluble inclusion complexes with the β-cyclodextrin. It was also observed that the β-cyclodextrin complexes may exhibit higher dissolution rate than the pure drug and their corresponding physical mixtures. The wetting time of solid dispersion by cogrinding method were evaluated and was in the range between 5.15 sec to 6.54 sec, it was found that the solid dispersion able to wet within a limited set of seconds in predetermined time for enhancement of solubility at pH 6.8 phosphate buffer.

CONCLUSIONS

This innovative strategy holds promise for the advancement of pharmaceutical technology and enables the development of more effective drug formulations that overcome the limitations of poorly soluble drugs, thereby leading to better

therapeutic outcomes for patients. The present study offers remarkable potential for revolutionizing drug delivery systems and ushers in the era of innovative medicines characterized by increased therapeutic efficacy, improved patient adherence and improved overall health outcomes.The solubility studies of drug β-CD systems in water at 25°C revealed that the solubility of drug increased linearly for the preparation of complexes by kneading method. Solid inclusion complexes of drug were prepared by kneading method appeared that the solubility behaviour of the material was modified by altering its surrounding environment.

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