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RIVAROXABAN SOLID DISPERSIONS FOR DISSOLUTION ENHANCEMENT AND FORMULATION OF MOUTH DISINTEGRATING TABLETS

Kalki Ranjan Priyadarshan, Asish Sahu*, Anjan Kumar Mahapatra,
K. A Chowdary, Ajit Nahak, Ruchita Kumari Patra

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ABSTRACT
Background: Work is carried out to improve rivaroxaban's dissolution rate (DR) and develop mouth-disintegrating tablets for rapid onset of action**. Objectives:** The work objective was to improve the dissolution rate of rivaroxaban using PEG 6000 by preparing its solid dispersions (SDs) further to prepare mouth-disintegrating tablets (MDTs). **Methods:** Methods like physical mixing, melting, and solvent evaporation were used to prepare SDs at 1:0.5, 1:1, and 1:1.5 w/w ratios of rivaroxaban with PEG 6000 were prepared. Differential scanning calorimetry (DSC) and Infrared spectroscopy (IR) were used to characterize the SDs. The selected solid dispersion at an appropriate drug: carrier ratio was used to develop MDTs by direct compression, using super disintegrants. **Results:** The SDs show improved solubility and rate of dissolution. SDs developed using a melting or solvent evaporation technique showed a more than two-fold increase in dissolution rate. In the dissolution study, after 60 min, the pure drug dissolved 45 %, while the prepared SDs showed almost more than 90 % within the same period. No significant drug carrier interaction was observed in the IR and DSC studies. However, minor shifts in peak values were observed for the characterization of functional groups in the drug structure. **Conclusions:** Formulation of solid dispersions of the drug with PEG 6000 is a successful approach for the dissolution rate improvement of rivaroxaban. This work for dissolution rate improvement of rivaroxaban using PEG 6000 showed significant improvement in dissolution rate at a 1:1 w/w ratio prepared by solvent evaporation method, which was further selected for mouth disintegrating tablet formulation.

INTRODUCTION

For most of the solid dosage forms, the oral route is considered a relatively practical and simple method of administration; however, the dissolution rate reduces the bioavailability of poorly soluble drugs and becomes one of the primary issues in developing dosage forms of drugs included in BCS class II and class IV [1]. The pharmaceutical industry has recently encountered many difficulties in formulating drugs with poor

*Royal College of Pharmacy and Health Sciences, Berhampur-760002, Odisha, India

***For Correspondence:** **asishsahu24@gmail.com**

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aqueous solubility, such as rivaroxaban. These drugs have low solubility, which limits their bioavailability despite their therapeutic potential [2]. Rivaroxaban is an oral anticoagulant (blood thinner). The IUPAC refers to the compound rivaroxaban as methyl thiophene-2-carboxamide. It is marketed as Xarelto [3]. Rivaroxaban is a non-vitamin K antagonist factor of Xa inhibitor. It is used as an anticoagulant for treating deep vein thrombosis with a recommended maximum dose of up to 20 mg once a day. It is needed to be administered at high doses as it has a very low solubility [4]. Solid dispersion is a technique that entails dispersing one or more active components in a solid state within an inert carrier or matrix. Because it is easy, effective, and affordable, it has consistently been shown to be a productive method for increasing the solubility of poorly soluble drugs in terms of dissolution and bioavailability [5]. Solid dispersions (SDs) result from dispersing poorly soluble active pharmaceutical ingredients (API) in an inert carrier matrix followed by melting or evaporation of solvent to obtain a solid state. [6]. Using the solid dispersion technique, we can achieve an improved dissolution rate, particle size reduction, and wettability after converting the drug from its crystalline form into amorphous by dispersing it in a carrier [7]. PEGs with a molecular weight range of 1500-20000 are utilized to prepare SDs. The increase in molecular weight increases viscosity, resulting in improved dissolution [8]. The aim is to investigate the dissolution rate of SDs of rivaroxaban with PEG 6000, their dissolution rate studies, and characterization by conducting IR spectroscopy and DSC, as less work is reported on solubility improvement of rivaroxaban and particularly by SD method using PEG 6000.

MATERIALS AND METHODS

Materials

A gift sample of rivaroxaban was received from Dr. Reddy's Laboratories (Hyderabad). As gift samples, PEG 6000 was obtained from Clariant GmbH, Germany. SLS was purchased from Merck Chemicals, Ltd. (Mumbai). Crospovidone, sodium starch glycolate, Ac-di-sol, and PEG 6000 (fine powder) were obtained from Alembic Pharmaceutical Ltd. as gift samples. Microcrystalline cellulose, pearlitol SD 200, were purchased from Finar Chemicals Ltd. Ahmedabad, Aerosil was purchased from Thomas Baker Chemicals Pvt. Ltd, Mumbai. Methanol was purchased from Pallav chemicals and solvents Pvt. Ltd., Tarapur, Bolsar. The other chemicals utilized for the experiment were of analytical grade.

Methods

Linear Plot

The linear plot was obtained by preparing standard drug solutions from 5-40 µg/mL using 0.5 % SLS in acetate buffer pH 4.5. UV spectrophotometry was used to determine $\lambda_{max.}$ The observed λ_{max} was 250 nm.

Preparation of solid dispersions

PEGs of high molecular weight are solids, and while taking more amount in the SDs, there may be wastage of the SDs while passing through the small mesh size sieves, resulting in wastage of drug or carrier. Moreover, these perfect hydrophilic carriers enhance satisfactory dissolution rates at low concentrations. The ratios 1: 0.5, 1:1, and 1: 1.5 were used to prepare the SDs of rivaroxaban with PEG 6000 by melting, physical mixing (PM), and solvent evaporation (SE) method. Using the melting method, upon a heating mantle, the drug and PEG 6000 were melted and kept at a temperature higher than the drug's and carriers' melting point, followed by rapid cooling till it solidified. The SDs preparation details are given in Table 1.

SE Method

The drug and PEG 6000 were taken at ratios of 1:0.5, 1:1, and 1:1.5 w/w. The drug and polymer were taken in a beaker, a small amount of ethanol was added to ensure their solubility and the solvent was removed by exposure to low temperature.

Table 1: SDs of Drug: PEG 6000 (w/w ratio)

Carrier (C)	Drug (D): Carrier (C)	Preparation Method
PEG 6000	1:0.5	PM
	1:1	
	1:1.5	
PEG 6000	1:0.5	SE
	1:1	
	1:1.5	
PEG 6000	1:0.5	FM
	1:1	
	1:1.5	

Percentage Drug Content

Percent drug content was obtained by preparing 20 and 30 µg/mL solutions by taking the drug equivalent to 50 mg from the SDs (treated as test solutions). The absorbance value of these test solutions was compared with the absorbance value of 20 and 30 µg/mL standard solutions obtained by taking the pure drug

(values obtained in preparation of linear plot). The test and standard absorbance ratio was multiplied by a hundred to get the percentage drug content.

***In vitro* dissolution studies**

Rivaroxaban and its SDs dissolution rate were determined using a USP type II (Paddle) apparatus. 900 mL acetate buffer of pH 4.5 was used as a dissolution medium, added with 0.5% w/v of SLS, following 50 rpm at 37± 0.5ºC. Samples of 5 mL were withdrawn using a syringe attached with a filter of 0.45µm at regular intervals. The absorbance was measured at 250nm to quantify rivaroxaban [9].

IR Spectroscopy Studies

A drug and carrier interaction study used IR spectroscopy (Shimadzu, Japan, FTIR-8400S) to obtain both spectra. Samples were made using KBr discs and scanned from 400-4000 cm^{-1}.

DSC Studies

The thermal behavior of the drug carrier used in the inclusion complexes was studied using a differential scanning calorimeter (DSC 4000, Perkin Elmer, America). A sample of 5 mg was kept in an Al pan and sealed. The isothermal study process was maintained at 40°C/m and a 25 ml/ m flow rate at a temperature range of (5-300 °C) in an atmosphere of N_2 as purge gas [10].

Formulation of mouth-disintegrating tablets

Due to its simplicity, ability to avoid pain, adaptability to accommodate various drugs, and, most importantly, patient compliance, the oral route of administration is the most accepted route. Many patients during treatment face difficulties in swallowing tablets and capsules, specifically in the case of elderly, pediatric, and geriatric resulting in patient non-compliance [11]. Intra-oral absorption can be achieved by dispersion and absorption within the oral cavity, which helps bypass the first-pass effect [12]. Mouth Disintegrating tablets (MDTs) are designed to break and disperse in seconds in the oral cavity without water, offering an effective and convenient suspension for patients [13]. The development of MDTs addresses several critical issues associated with conventional oral dosage forms. From a pharmaceutical perspective, the formulation of MDTs involves sophisticated techniques to ensure quick disintegration, pleasant taste, and adequate stability.

In the mouth-disintegrating formulation, super-disintegrants are considered as they induce swelling and water absorption, resulting in quick disintegration [14]. Ensuring mechanical strength to endure handling with packaging while preserving quick disintegration properties requires a delicate balance. Additionally, achieving taste masking, especially for bitter drugs, is essential to ensure patient acceptability.

Formulation of rivaroxaban MDT

MDTs of rivaroxaban were made using an equivalent amount of drug (20 mg) in the SDs of PEG 6000 by direct compression method using an 8 mm flat-faced punch. The formulation table is given in the Table 2.

Table 2: Formulation of rivaroxaban mouth-disintegrating tablets (Batch size 100 tablets)

S. No.	Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Rivaroxaban SDs (equivalent to 20 mg of drug)	40	40	40	40	40	40	40	40	40
2.	Crospovidone	10	20	30	-	-	-	-	-	-
3.	Sodium starch glycolate	-	-	-	10	20	30	-	-	-
4.	Croscarmellose sodium (Ac-di-sol)	-	-	-	-	-	-	10	20	30
5.	Pearlitol SD 200	100	100	100	100	100	100	100	100	100
6.	Avicel PH104	95	85	75	95	85	75	95	85	75
7.	PEG 6000 (Fine Powder)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8.	Colloidal SiO_2	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Total weight	250	250	250	250	250	250	250	250	250

Rivaroxaban is taken as the API, while crospovidone, sodium starch glycolate, and croscarmellose sodium (Ac-di-sol) are taken as super disintegrants at 4%, 8%, and 12%. Pearlitol SD 200 is a spray-dried form of mannitol; it has a free flow & is a directly compressible excipient. Avicel PH104, known as microcrystalline cellulose, is a diluent. PEG 6000 (Fine powder) is used as a lubricant to quickly eject the tablets from the die cavity. Colloidal SiO_2 is used as a glidant.

Evaluation tests for tablets [15]

Hardness

The hardness of the tablets is a critical parameter in the formulation of MDTs. More hardness will affect the dispersion time, and less hardness may not withstand mechanical stress during shipping and handling. Hence, the hardness was maintained between 2.5 and 3 kg/cm^2 to meet the required properties of MDTs.

Friability

Friability was tested using a Roche friabilator, taking 25 tablets, and rotating for 4 minutes, and the weight loss was determined.

Disintegration test

The disintegration test for tablets was performed by taking 6 tablets in a disintegrating test apparatus and running the DT apparatus to note the tablets' DT.

Test for Dispersion

The dispersion test is a critical evaluation parameter for MDTs. The same two tablets were in a beaker containing 100 mL of water. When required, the contents were stirred gently at the top and waited for 3 minutes. After 3 minutes, the content was poured through a 710 µm sieve (22 mesh), and no residue remained over the sieve. This indicates that the tablet passes the dispersion test.

Drug content uniformity test

The drug content of the prepared tablets of each batch was determined. Twenty tablets were taken, weighed, and finely ground from each batch. An amount of this powder equivalent to 5mg of the drug was accurately weighed, suitably dissolved, diluted, and analyzed by UV method at 231nm. UV-Vis spectrophotometer (Shimadzu-1800) was used, and the analysis method was developed to assay drug content in the tablets.

Weight variation test

The weight variation was determined on 20 tablets using an electronic balance (Sartorius, 0.001g sensitivity).

Wetting time

Five circular tissue papers (10cm diameter) were placed in a petri dish of 10 cm diameter, containing 10mL of water added with methylene blue (a water-soluble dye). A tablet was carefully placed on the surface of the tissue paper. The time required for water (colored) to reach the upper surface of the tablets was noted as the wetting time.

RESULTS AND DISCUSSION

The rivaroxaban linear plot was obtained, as shown in Figure 1, along with the R^2 value and regression equation.

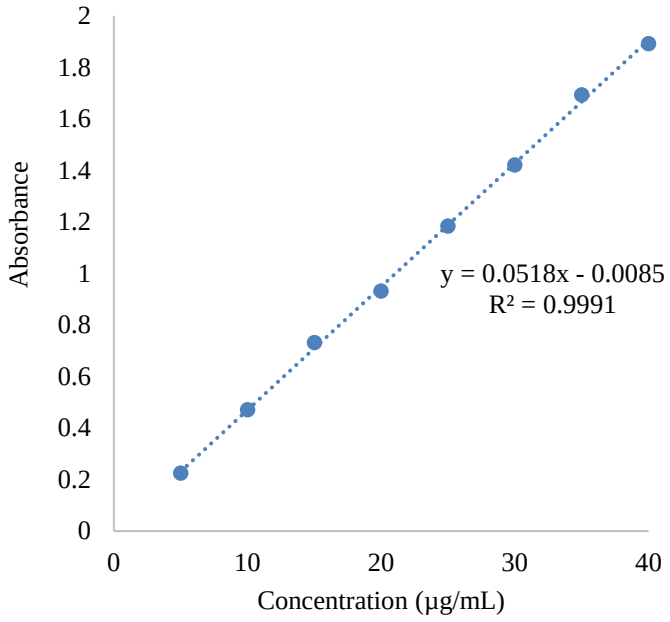

Figure 1: Linear plot of rivaroxaban

***In vitro* dissolution studies**.

Tables 3 and 4 provide in vitro dissolution data for the drug up to 60 m study.

Table 3: *In vitro* dissolution data of rivaroxaban (Pure drug) and rivaroxaban SDs (PM)

Time (m)	% DR (Pure Drug)	% Drug release (PM)		
		1:0.5	1:1	1:1.5
0	0	0	0	0
5	24.14 ± 1.92	27.41 ± 1.33	29.32 ± 1.65	30.39 ± 2.24
10	28.62 ± 2.12	31.82 ± 2.64	32.61 ± 1.24	33.54 ± 2.53
20	32.37 ± 1.82	34.51 ± 2.98	34.54 ± 2.89	36.77 ± 3.21
30	36.92 ± 1.68	38.71 ± 2.14	39.22 ± 2.59	40.63 ± 2.95
45	39.49 ± 1.98	43.34 ± 1.88	44.60 ± 2.87	45.85 ± 3.17
60	43.31 ± 2.21	48.83 ± 2.74	49.69 ± 2.14	50.82 ± 3.20

In vitro dissolution data of rivaroxaban drug, the % drug release was 43.31 % at 60 m.

In vitro dissolution data of rivaroxaban SDs (PM), the % drug release was 50.82 % at 60 m.

Table 4: *In vitro* dissolution data of rivaroxaban SDs (SE) and rivaroxaban SDs (Melting/Fusion)

Time (m)	% Drug release (SE)			% Drug release (F/M)		
	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5
0	0	0	0	0	0	0
5	38.63 ± 2.34	45.82 ± 1.34	48.93 ± 1.78	43.50 ± 2.13	48.87 ± 2.32	47.81 ± 2.71
10	42.35 ± 2.62	50.39 ± 2.76	52.87 ± 1.81	46.43 ± 2.34	59.92 ± 2.41	51.97 ± 2.36
20	47.42 ± 2.85	64.46 ± 1.93	69.52 ± 1.43	52.72 ± 2.26	64.57 ± 2.58	63.47 ± 1.88
30	54.84 ± 1.47	77.47 ± 1.75	77.70 ±1.85	55.32 ± 2.50	77.79 ±1.73	74.79 ± 1.32
45	60.92 ± 1.92	85.52 ± 1.90	88.41 ± 1.78	60.61 ± 2.49	84.53 ± 1.87	82.30 ±1.75
60	64.39 ± 2.18	94.92 ± 1.86	95.22 ± 1.31	63.35 ± 2.31	90.40 ± 1.62	92.22 ± 1.97

Mean value ± S.D. (n = in triplicate)

In vitro dissolution data of rivaroxaban SDs (SE), the % drug release was found to be 77.47 % at 30 m, 85.52 % at 45 m, and 94.92 after 60 m. *In vitro* dissolution data of rivaroxaban SDs (melting/ fusion), the % drug release was found ± 84.53 % at 45 m and 90.40 % after 60 m. The dissolution data in Tables 3 and 4 showed that SDs prepared by different techniques had better results than the pure drug. The data shows that PM at 1:1.5, SE 1:1, and F/M at 1:1 w/w ratio showed a better dissolution rate when compared to the other ratios by the same method. Hence, these selected ratios are considered in plotting the dissolution profile as a comparative study, as shown in Figure 2.

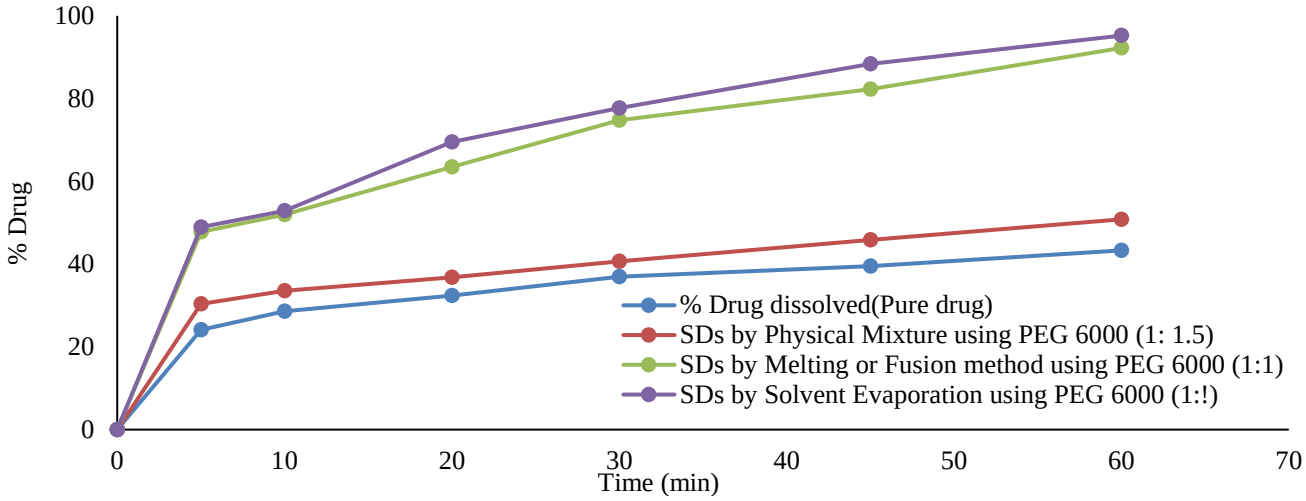

Figure 2: Comparative dissolution data of prepared SDs by different techniques

IR Spectroscopy

The result of the peaks observed is discussed as follows: in the IR spectra of rivaroxaban, the peaks at 3100 cm-1 are due to the C-H bond. 2914 cm^{-1} may be due to the presence of C-H bond. 1730 cm^{-1} is due to carbonyl group; 1100-1000 cm^{-1} peaks is due to C-O stretching. 900-600 cm^{-1} may be due to the aromatic rings. 769 cm^{-1} is due to aromatic C-Cl stretching. Similarly, for the drug carrier mixture, i.e., rivaroxaban and PEG 6000, the peaks at 3432 cm-1 for O-H stretching and 1730 cm-1 are due to stretching of the C=O group. Though there is a shift in peak values due to the formation of bonds for drug carrier complexes, these important peak values for drugs are still retained, indicating no significant interaction. The IR spectrum is given from Figure 3 to Figure 5.

DSC

The DSC analysis reveals the sharp endothermic (down) peak for rivaroxaban at 25.91°C, corresponding to its melting point and indicating its crystalline nature. But, in the SDs of the drug, there is no sharp peak; it is a broad peak with retention of melting points for the drug and PEG 6000, indicating compatibility, which indicates the homogeneous distribution of drugs in SDs. The thermograms are given below. The DSC thermogram is shown in Figure 6 to Figure 8

Drug content

The percentage drug content in SDs obtained by different methods like PM, M/F, or SE methods was found to be between 95-98 %. The results of evaluations for the prepared MDTs are given in Table 5

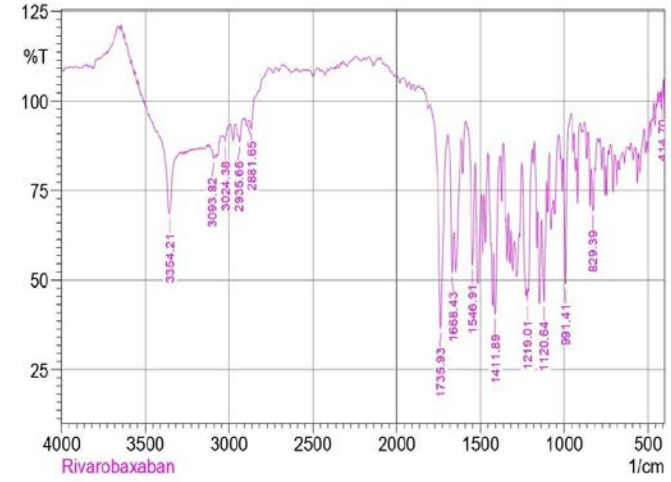

Figure 3: Rivaroxaban IR-spectrum

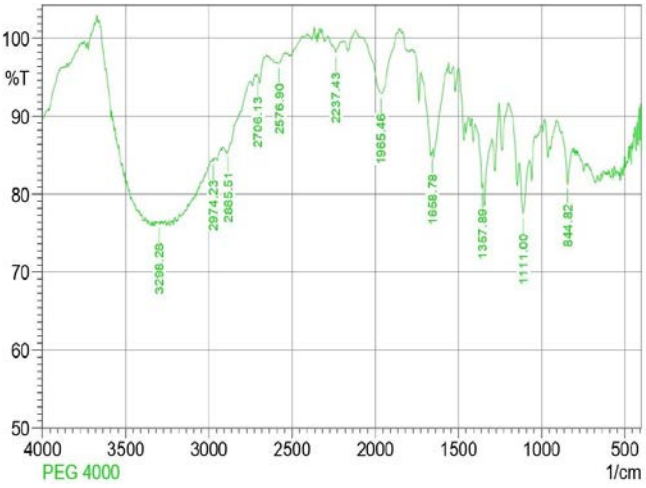

Figure 4: PEG 6000 IR-spectrum

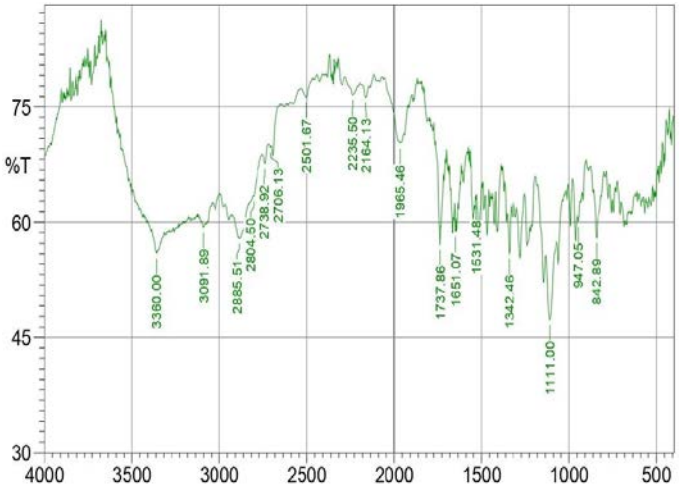

Figure 5: Rivaroxaban - PEG6000 SD by SE at 1:1 ratio IR-spectrum

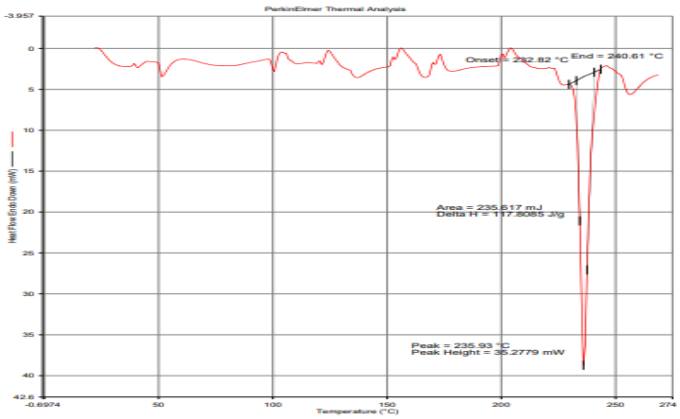

Figure 6: DSC for rivaroxaban

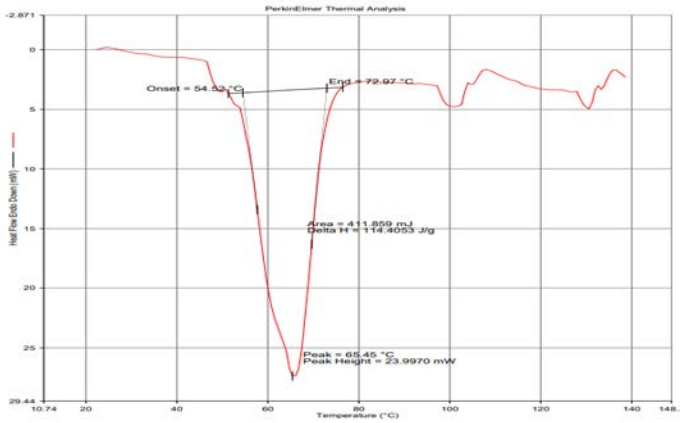

Figure 7: DSC-PEG 6000

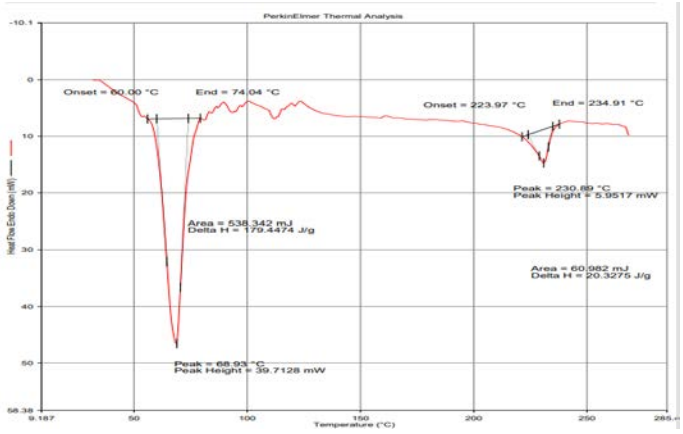

Figure 8: DSC-PEG 6000 + rivaroxaban (SE method)

DISCUSSION

The dissolution study of the prepared SDs using various methods and PEG 6000 indicates that solvent evaporation and melting or fusion methods significantly increase the rivaroxaban dissolution rate. Dissolution data was obtained for all the prepared SDs by all the methods (PM, M/F, SE) and at all ratios (1:0.5, 1:1. 1:1.5 w/w), and the results are given in Table 3 and Table 4. From the results, it was observed from the tabulated

data that the SDs prepared by PM at 1:1.5 w/w ratio and SDs prepared by M/F and SE methods at 1:1 w/w ratio showed an improvement in the dissolution rate compared to the pure drug. Though the dissolution rate is improved by physical mixing compared to the pure drug, it is only 50.82 %, hence not meeting the objective or dissolution criteria or requirements.

Table 5: Physical properties of compressed tablets

Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug content (%)	96.2	99.4	99.1	98.7	97.2	98.4	96.1	97.9	98.5
Weight variation (%)	5.0	4.2	4.9	4.3	5.2	5.4	6.3	4.2	4.5
Hardness (kg/cm^2)	2.9	2.6	2.8	2.7	2.5	2.8	2.7	2.6	2.5
Friability (%)	0.5	0.7	0.6	0.5	0.7	0.5	0.6	0.5	0.7
Wetting Time (sec)	78	31	37	83	72	67	80	73	60
Disintegration time (sec)	110	40	41	120	105	95	130	102	94

The dissolution rate of SDs prepared by M/F and SE method at 1:1 meets the dissolution criteria as they showed more than 88 % in SDs by SE method and 84 % in the case of SDs by M/F. A comparative dissolution profile for drug, SDs prepared by PM at 1:1.5 w/w, SDs by M/F, and SE method at 1:1 w/w ratio is given in Figure 2. The drug rivaroxaban showed a dissolution rate of approximately 43 % after 60 m. The solubility was more than 85 % at 45 m in both melting and solvent evaporation methods at 1:1 w/w drug-to-carrier ratio, and more than 90 % dissolution was found after 60 m. These results meet the dissolution requirements of USP. Though the results of both the M/F and SE methods are satisfactory, the dissolution rate is still better for SDs using the SE method. Moreover, in the M/F technique, the drug and carrier are heated to melt or fuse. Hence, there is a chance of degradation of the drug if the mixture is overheated. Hence, it is realized that the SE technique is more convenient than the melting technique, for which SDs obtained by the SE method at 1:1 w/w are used in the formulation of MDTs.

Studies of DSC and IR support the absence of significant drug-carrier interaction. The percentage drug content for all the MDTs (F1-F9) was between 96 % and 99 %, of which F2 showed the highest concentration of 99.4 %. The formulated MDTs (F1-F9) passed the test for weight variation. The dispersion test was passed for the tablets of F2 and F3, with a dispersion time of less than 3 m. The Tablets of F6 and F9 also passed the dispersion test, but they showed more disintegration time when compared to the tablets of F2 and F3. Hence tablets of F2 and F3 were considered better. While comparing the tablets of F2 and F3, tablets of the F2 formulation show less disintegration time at a lower concentration of the super disintegrant (i.e., 8 %) than F3 (i.e., 12 %). Friability in all the formulations (F1-F9) was less than 1%. Based on the results obtained, F2 is considered the optimized formulation, having a drug concentration of 99.4% and a disintegration time of 40 seconds, showing satisfactory results with crospovidone at 8 % of the tablet weight, whose mechanism involves swelling and burst to release. The study observed that F2 formulations are fulfilling the objectives of working at an optimum concentration of super disintegrant and other ingredients.

CONCLUSIONS

Using SDs of rivaroxaban with PEG 6000 can improve the dissolution rate of rivaroxaban. The IR and DSC studies observed No interaction between rivaroxaban and PEG 6000. A change in the state of rivaroxaban from crystallinity to amorphous was observed during the DSC studies in their solid dispersions. MDT formulation (F2) was selected as optimized and contained 8 % crospovidone as a super disintegrant. Such an approach can be exploited to improve the dissolution of other low-soluble drugs. A critical limitation of the MDTs is that they may not withstand mechanical stress during handling and shipment because the tablets have less hardness. Moreover, the super disintegrants used in the formulation of MDTs are hygroscopic, and particularly crospovidone is highly hygroscopic. Hence, proper packaging, container system selection, and storage should be rationally selected to not affect the tablets' disintegration time, dissolution rate, and stability.

Dysphagia is a common age-old problem associated with conventional tablets. MDTs will be convenient for administration where the tablet will disintegrate in the saliva of the oral cavity, forming a suspension that can be swallowed easily by pediatrics or geriatrics as the case of its use. The aim is to conduct an in vivo study of the performance of the prepared MDTs as a future scope of study and research.

FINANCIAL ASSISTANCE
Nil

CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Kalki Ranjan Priyadarshan, Ashish Sahu, and Anjan Kumar Mahapatra designed the study and experimental work. K. A. Chowdary was involved in data collection and analysis. Ajit Nahak and Ruchita Kumari Patra drafted and edited the manuscript content and reviewed the draft. All the authors have made near or equal contributions to the work and publication of this manuscript.

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