International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 2, 2023

Original Article

SOLUBILITY ENHANCEMENT OF RIVAROXABAN BY SOLID DISPERSION WITH POLYETHYLENE GLYCOL 4000

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Received: 27 Oct 2022, Revised and Accepted: 12 Dec 2022

ABSTRACT

Objective: The aim of the work was to enhance the dissolution rate of rivaroxaban by preparing its solid dispersions (SDs) using hydrophilic carrier PEG 4000.

Methods: The SDs of rivaroxaban with PEG 4000 were prepared at 1:1, 1:2 and 1:3 w/w ratios by physical mixing, melting and solvent evaporation techniques. The prepared solid dispersions were characterized by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

Results: Both the solubility and dissolution rate of the drug in these formulations were increased. The used hydrophilic carriers showed a more than two-fold increase in dissolution rate in their prepared solid dispersions by melting or solvent evaporation techniques. The pure drug rivaroxaban as the pure drug shows a dissolution rate of nearly 39 % after 60 m, whereas the solid dispersions by melting or solvent evaporation showed 90% of dissolution after 60 m. The FTIR spectroscopic and DCS thermal studies showed the compatibility of rivaroxaban and the absence of well-defined drug polymer interactions, though the shift in peaks was observed due to the formation of new bonds.

Conclusion: Formulation of solid dispersions of drug with hydrophilic carriers is a successful approach for solubility or dissolution rate enhancement of low soluble drug(s). In this work for solubility enhancement of rivaroxaban the hydrophilic carrier PEG 4000 showed significant solubility enhancement.

Keywords: Solid dispersions, Dissolution rate, PEG 4000, Hydrophilic carriers, Physicochemical characterization

DOI: https://dx.doi.org/10.22159/ijap.2023v15i2.46687. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

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 [1]. 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 [2].

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. The action of rivaroxaban is irreversible [3].

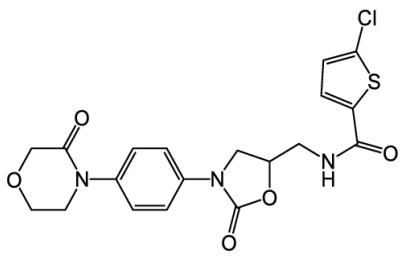

Fig. 1: Rivaroxaban

Among the various approaches to improve solubility, the solid dispersion techniques has often proved to be the most successful in improving the dissolution and bioavailability of low soluble active pharmaceutical ingredients (APIs) because it is simple, economic, and a successful approach [4]. Dispersion of poorly soluble drugs in an inert hydrophilic carrier or carrier matrix at solid state provided by the melting solvent, solvent evaporation method leads to products referred to as solid dispersions (SDs). These SDs provide the possibility of reducing the particle size of such drugs to nearly to a molecular level, to transform the drug from the crystalline to the amorphous (partial or complete) state, and/or to locally increase the saturation solubility. In other words, SDs improves the rate of bioavailability of poorly soluble drugs by increasing their saturation solubility in the gastrointestinal fluids. Polyethylene glycols (PEGs) with molecular weights of 1500–20000 are used for the preparation of SDs of drugs showing poor onset of absorption and bioavailability. Therefore, improvement in solubility and/or dissolution rate may lead to enhanced bioavailability leading to better therapeutic action [5].

As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. Polymers such as polyethylene glycols and poloxamers have been extensively used as carriers for dispersions due to their low melting point and their hydrophilic environment [6].

From an economical point of view low oral bioavailability results in wasting of a large portion of an oral dose and adds to the cost of drug therapy especially when the drug is an expensive one [7].

Although most of the drugs have encouraging experimental data obtained *in vitro*, the *in vivo* results have been disappointing. The attributes include poor absorption, rapid degradation, drug distribution to other tissues with high drug toxicities (anticancer drugs), poor solubility of drugs, and fluctuations in plasma levels owing to unpredictable bioavailability [8].

The primary objective of the present study is to investigate the solubility and dissolution rate of solid dispersions of the drug in PEG 4000. To this purpose, physical characterizations based on IR spectroscopy and differential scanning calorimetry (DSC) was

performed. Solubility analysis and dissolution studies were also carried out [9].

MATERIALS AND METHODS

Materials

Gift sample of rivaroxaban was received from Dr. Reddy's Laboratories, (Hyderabad, India). PEGs 4000 were received from Clariant GmbH, Germany as gift samples. Sodium lauryl sulfate (SLS) was purchased from Merck Chemicals, Ltd. (Mumbai). Distilled water was used for all dissolution experiments and all the other chemicals used were of analytical grade.

Methods

Analytical method

Analytical method for λ_{max} was determined by UV spectrophotometry preparing standard solutions of the drug (from 5-40 µg/ml) using acetate buffer pH 4.5 containing 0.5 % w/v SLS. The λ_{max} was found to be 250 nm with a coefficient of determination of 0.999.

Preparation of solid dispersions

The SDs of rivaroxaban with PEG 4000 at three different weight ratios of drug and polymer (1:1, 1:2 and 1:3) were prepared by physical mixing, melting or fusion and solvent evaporation method. In the melting method, the required amount of drug and PEG 4000 were melted in a beaker on a heating mantle maintained at a temperature above to a temperature of the corresponding melting point of the drug and the used hydrophilic carriers. The mixture was cooled rapidly by placing the beaker on an ice bath with rapid stirring till the molten and liquified mixture solidified. The dispersions were stored for 48 h in a desiccator containing anhydrous calcium chloride. The solid dispersion was then scrapped and sieved through a 30-mesh sieve and stored in a screw-cap vial until further studies [10].

Solvent evaporation

For solvent evaporation, the drug and PEG 4000 was taken at 1:1, 1:2 and 1:3 w/w ratios. The polymer was taken in a beaker with the drug and mixed with a minimum amount of ethanol to make both the drug and carrier soluble in the common solvent. After that, the solvent was removed with the help of heat at low temperature to remove the solvent. The obtained solid dispersions were stored for 48 h in a desiccator containing anhydrous calcium chloride, then scrapped and sieved through a 30-mesh sieve and stored in a screw-cap vial until further studies [11].

Physical mixture

The physical mixtures (PMs) were prepared by thoroughly mixing the required amount of drug with PEGs 4000 in a mortar. The resulting mixtures were sieved through a 30-mesh sieve. The mixtures were stored in a screw-cap vial until further studies [12].

In vitro dissolution studies

Dissolution studies of the rivaroxaban, and its solid dispersions were performed by using the U. S. Pharmacopoeia (USP) model digital tablet dissolution test apparatus type-2 (Lab India, Mumbai) at the paddle rotation speed of 50 rpm in 900 ml of pH 4.5 acetate buffer as dissolution media containing 0.5 % w/v of SLS at 37±0.5 °C. The SDs of equivalent to 10 mg of the rivaroxaban was weighed using a digital balance (Sartorius) and added into the dissolution medium. At the specified time intervals, 10 ml samples were withdrawn by using a syringe filter (0.45µm) (Sepyrane, Mumbai) and then assayed for the rivaroxaban, content by measuring the absorbance at 250 nm using the UV-visible spectrophotometer (Shimadzu UV-1700) [12]. Fresh medium of 10 ml which was maintained at 37 °C, was added to the dissolution medium after each sampling to maintain sink condition. Dissolution studies were performed in triplicate (n=3), and calculated mean values of cumulative drug release were used while plotting the release curves [13, 19].

Fourier-transform infrared spectroscopy

The FTIR spectra were obtained by using an FTIR (IR-Affinity-1, Shimadzu, Japan). The samples (rivaroxaban or SDs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 2 cm^{-1}, from 4000 to 400 cm^{-1} [14].

Differential scanning calorimetry

The DSC measurements were performed on a DSC-4000, Perkin Elmer, Singapore differential scanning calorimeter with a thermal analyzer. The samples were placed in sealed aluminum pans before heating under nitrogen flow (20 ml/min) at a scanning rate of 10 °C min^{-1} from 50 to 300 °C. An empty aluminum pan was used as a reference [15-17].

Table 1: Preparation of SDs with different methods at w/w ratios of PEG 4000

Polymers use	Drug: polymer	Method of preparation
PEG 4000	1:1	PM
	1:2	
	1:3	
PEG 4000	1:1	SEM
	1:2	
	1:3	
PEG 4000	1:1	FM
	1:2	
	1:3	

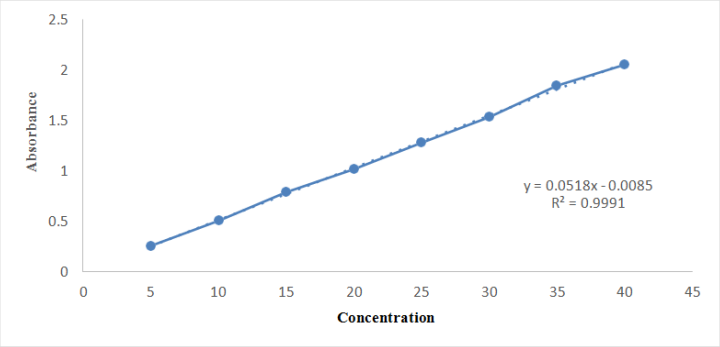

Fig. 2: Linear plot of rivaroxaban

RESULTS AND DISCUSSION

The linear plot of rivaroxaban was obtained by using acetate buffer pH 4.5 containing 0.5 % SLS. Standard solutions were prepared from 5 to 40 µg/ml and their corresponding absorbance values were determined at 250 nm. From the result, it was found that its linearity is maintained at the concentration range of 5-40 µg/ml, hence follows Beer-Lambert's Law [18].

In vitro dissolution studies

The dissolution of poorly soluble drugs requires dissolution media that are different from those normally used for water-soluble drugs. One of the techniques that have been found to be useful in the dissolution of insoluble drugs is the incorporation of a small amount of surfactant in the dissolution medium. The use of surfactants in dissolution systems may be physiologically more meaningful due to the presence of natural surfactants like bile salts in the gastrointestinal tract. The ability of surfactants to accelerate the *in vitro* dissolution of low water-soluble drugs has been attributed to wetting, micellar solubilization, and/or deflocculation. It is easy to understand that a biorelevant medium will need similar surface activity as bio-fluids [19].

Dissolution of pure rivaroxaban and all prepared systems (SDs) was carried out in water and acetate buffer pH 4.5 containing SLS (0.5 % w/v). Dissolution studies were performed for 60 min. It is evident that the dissolution of pure rivaroxaban is very low 37.94 %, within 60 min. Solid dispersions of rivaroxaban with PEG 4000 considerably enhanced dissolution rates compared to the pure rivaroxaban and physical mixtures. The graphical presentation of the dissolution profile of pure rivaroxaban and the SDs over a period of 60 min is shown in fig. 3. The dissolution data for pure rivaroxaban is given in table 2.

Table 2: Dissolution rate of rivaroxaban

Time (min)	% Drug dissolved
0	0
5	22.65±2.14
10	25.58±1.93
20	28.45±2.74
30	31.40±2.22
45	35.86±2.94
60	37.94±1.98

The values are presented as mean±SD (n = 3); for pure drug dissolution, the % drug dissolved was found to be 37.94 % at 60 min.

Dissolution rate (i.e., % drug dissolved with time) studies

Table 3: Dissolution rate of rivaroxaban SDs by the physical method using PEG 4000

Time (min)	% Drug dissolved		
	1:1	1:2	1:3
0	0	0	0
5	24.67±1.33	26.43±2.56	29.34±2.11
10	28.11±2.64	29.72±2.14	31.69±2.46
20	32.45±2.98	31.67±1.62	35.84±2.59
30	34.65±2.14	35.33±3.12	38.54±2.73
45	37.27±1.88	39.54±2.69	42.24±2.77
60	43.99±2.74	44.75±2.88	46.78±2.68

The values are presented as mean±SD (n = 3), In the dissolution rate of rivaroxaban SDs by the physical method using PEG 4000 the % of drug dissolved was found to be 46.78 % at 60 m.

Table 4: Dissolution rate of rivaroxaban SDs by melting or fusion method using PEG 4000

Time (min)	% Drug dissolved		
	1:1	1:2	1:3
0	0	0	0
5	41.45±2.23	43.93±2.11	45.93±2.12
10	44.48±2.13	46.87±2.54	49.87±2.11
20	49.67±2.49	60.62±2.31	62.52±1.98
30	54.38±2.94	78.74±1.89	71.74±1.54
45	59.56±2.33	83.54±1.96	84.41±1.89
60	62.41±2.14	90.33±1.54	92.12±1.88

The values are presented as mean±SD (n = 3), In **the** dissolution rate of rivaroxaban SDs by melting or fusion method using PEG 4000 the % drug dissolved was found to be±83.54 % at 45 m and more than 90 % after 60 m.

Table 5: Dissolution rate of rivaroxaban SDs by solvent evaporation using PEG 4000

Time (min)	% Drug dissolved		
	1:1	1:2	1:3
0	0	0	0
5	37.78±2.11	44.91±2.01	47.93±1.63
10	40.23±1.87	49.30±1.87	49.87±1.98
20	44.54±1.57	63.11±2.33	67.52±1.55
30	51.58±2.32	72.33±2.55	74.70±1.82
45	61.19±2.11	85.61±2.74	87.41±1.94
60	63.24±1.98	91.26±2.42	94.22±1.11

The values are presented as mean±SD (n = 3), In dissolution rate of rivaroxaban SDs by solvent evaporation using PEG 4000 % drug dissolved was found to be 85.61 % at 45 m and 91.26 after 60 m, A comparative dissolution rate of optimized SDs of rivaroxaban with PEG 4000 by different techniques is shown in fig. 3.

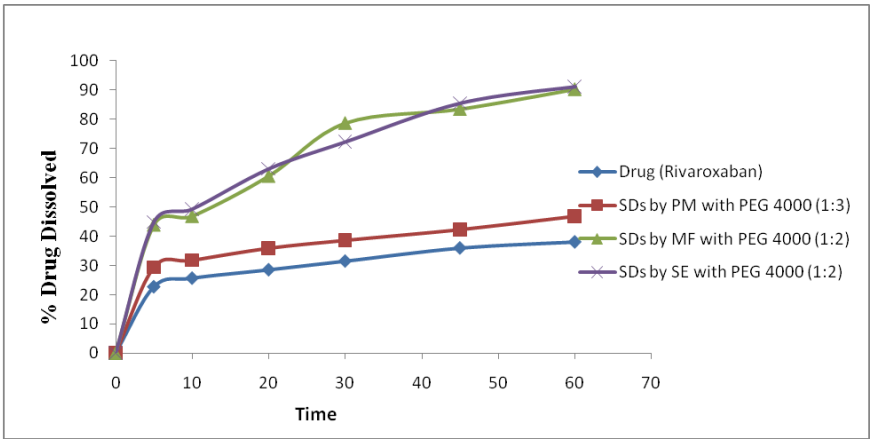

Fig. 3: Comparative dissolution rate of optimized SDs of rivaroxaban with PEG 4000 by different techniques, the values are presented as mean±SD (n = 3)

Fourier-transform infrared spectroscopy

The interaction between the drug and the carrier often leads to identifiable changes in the IR profile of SDs. The IR spectra of SDs were compared with the standard spectrum of Rivaroxaban. IR spectra of pure rivaroxaban reveal the presence of peak at 3100 cm^{-1} indicates the presence of an aromatic C-H bond. Peak at 2914 cm^{-1}indicates the presence of C-H bond. Presence of peak at 1730 cm^{-1} indicates the presence of carbonyl group, Peaks in the range of 1100-1000 cm^{-1} confirms C-O stretching. IR spectra in the range of 900-600 cm^{-1} indicate the presence of aromatic rings. Spectrum at 769 cm^{-1} was due to aromatic C-Cl stretching. O-H stretching at 3432 cm^{-1} for OH and C=O stretching at 1730 cm^{-1} for the drug in the solid dispersions have not undergone interaction and individual peak characteristics are retained, indicates there is no interaction between the drug and the carrier.

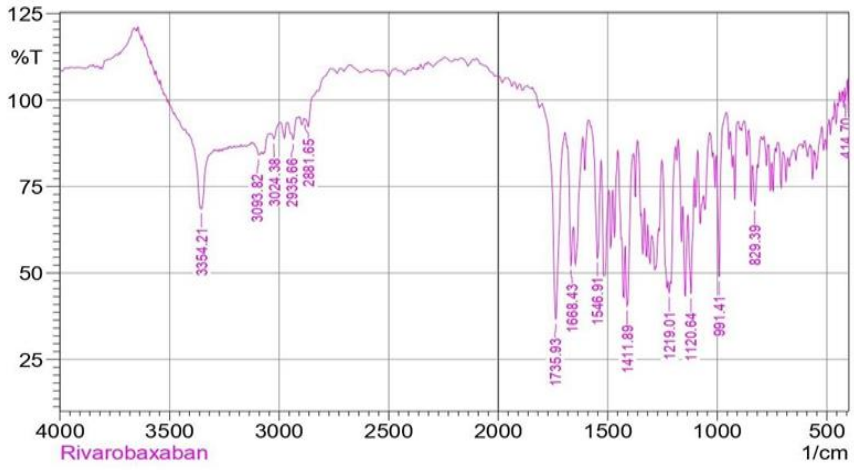

Fig. 4: FTIR spectra of rivaroxaban

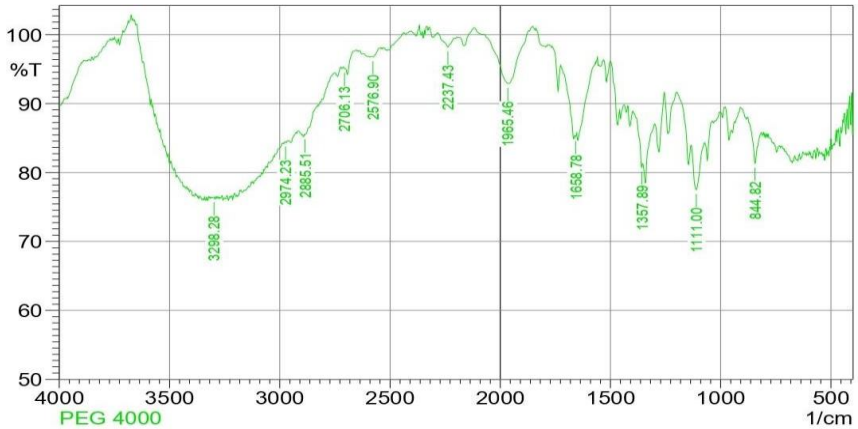

Fig. 5: FTIR spectra of PEG4000

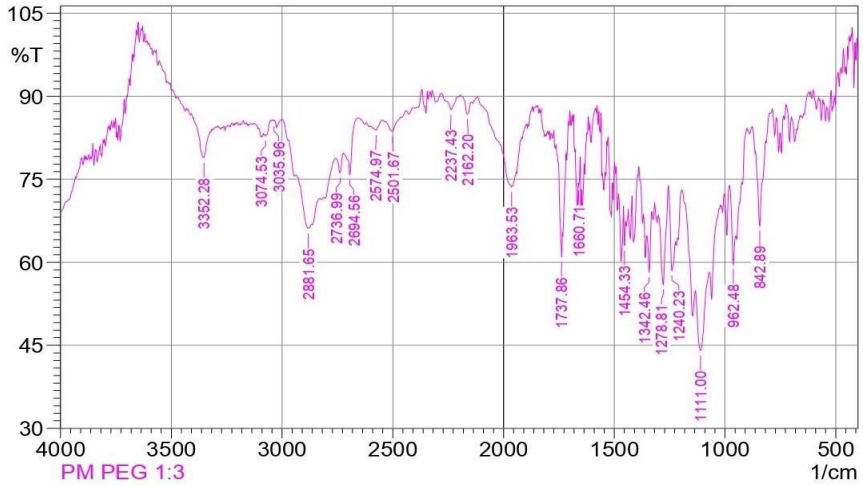

Fig. 6: FTIR spectra of SD of rivaroxaban with PEG4000 (PM 1:3)

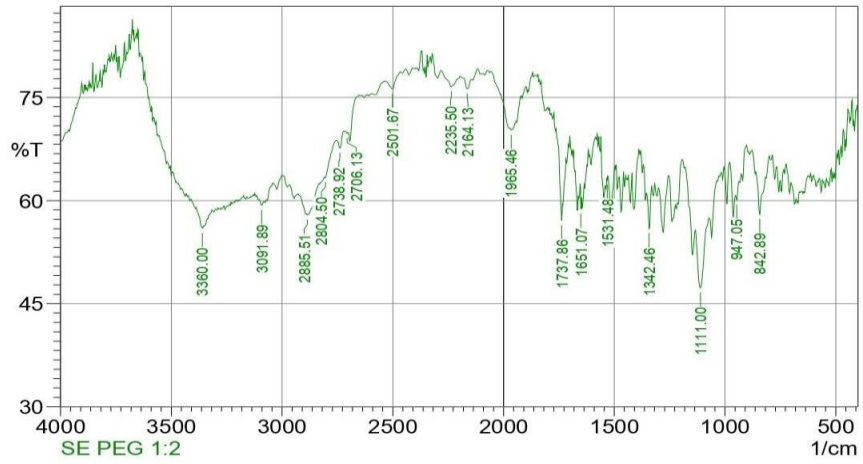

Fig. 7: FTIR spectra of SD of rivaroxaban with PEG 4000 (SE 1:2)

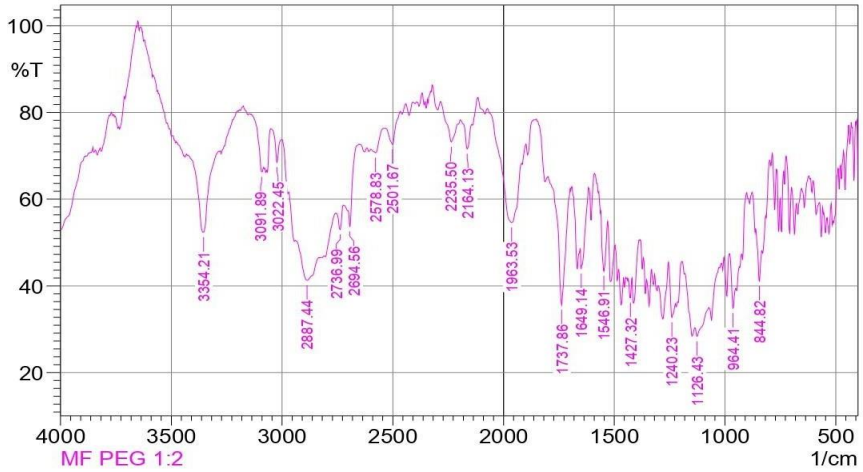

Fig. 8: FTIR spectra of SD of rivaroxaban with PEG 4000 (MF1:2)

Differential scanning calorimetry

Differential Scanning Calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic, and exothermic phase transformations). The single endothermic peak corresponding to its melting point was observed at 235.91 °C. Absence of a peak for the drug indicates that the drug is distributed homogenously in an amorphous state with in the solid dispersions without any interaction [20].

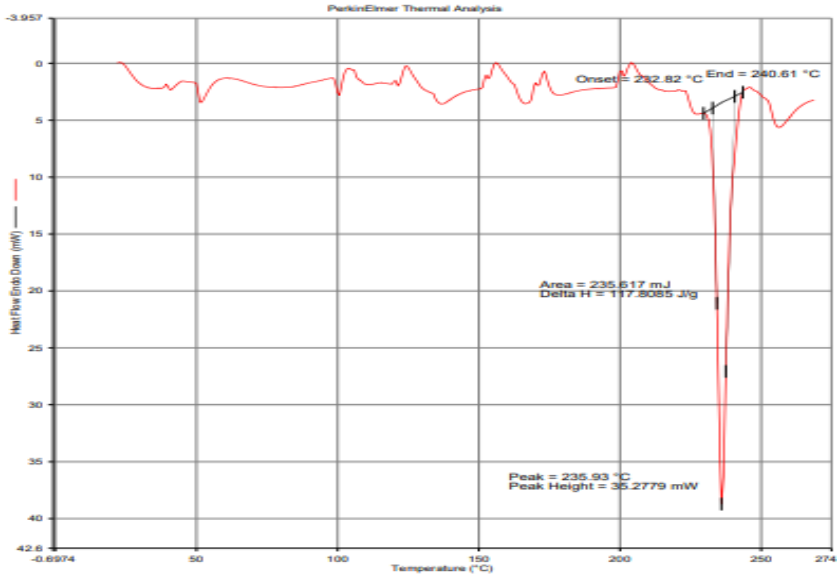

Fig. 9: DSC thermogram of rivaroxaban

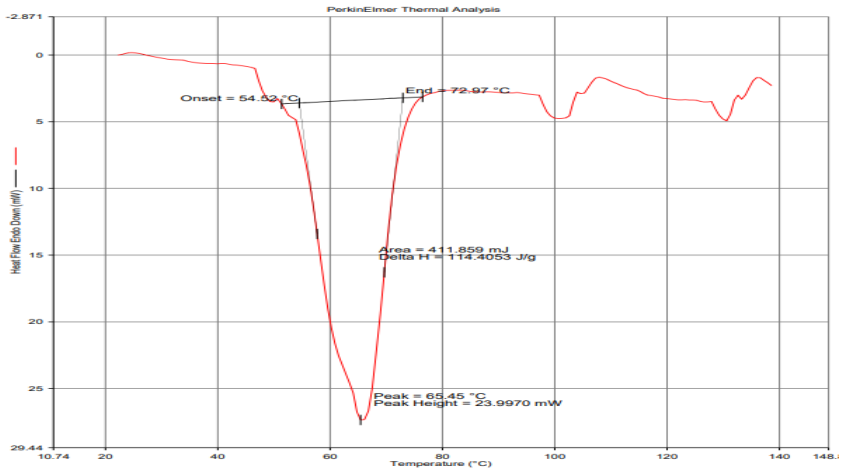

Fig. 10: DSC thermogram of PEG 4000

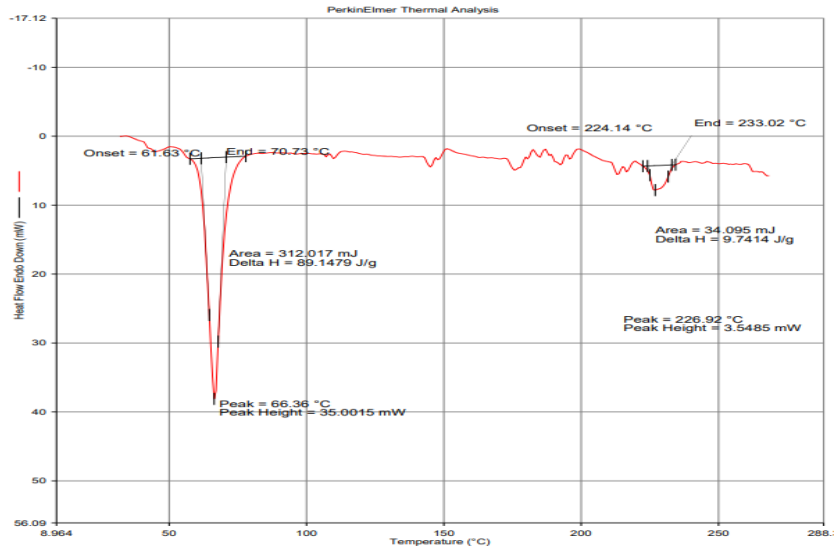

Fig. 11: DSC thermogram of PEG 4000 and rivaroxaban MF

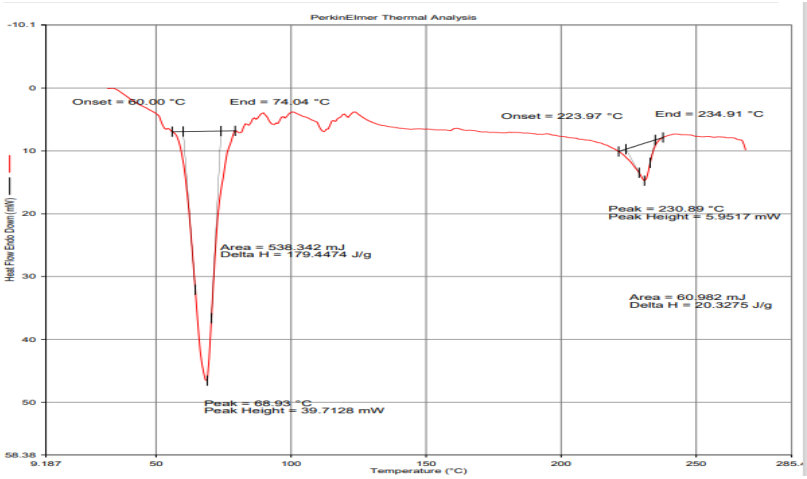

Fig. 12: DSC thermogram of PEG 4000 and rivaroxaban SE

It is observed from the dissolution study of the prepared solid dispersions by different techniques and at different ratios of hydrophilic carrier (PEG 4000), either melting or fusion technique and solvent evaporation technique shows significant enhancement of solubility of rivaroxaban as the pure drug shows a dissolution rate of nearly 39 % after 60 m. The weight ratio of 1: 2 can be considered optimum ratio to get the result of solubility or dissolution rate enhancement. In both the techniques; either melting or fusion technique and solvent evaporation technique for 1:2 drug-carrier ratio the solubility was found to be more than 75 % in 45 min, which meets the USP/NF requirements as a common dissolution tolerance, and more than 90 % dissolution is found after 60 min. The possible mechanism of increased dissolution rates of SDs have been proposed by Ford (1986) and include: reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability, molecular dispersion of the drug rivaroxaban in the carrier system, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the above-mentioned methods [21, 22]. The FTIR spectroscopic and DCS thermal studies showed the compatibility of rivaroxaban and the absence of well-defined drug polymer interactions, though shift in peaks observed due to the formation of new bonds.

CONCLUSION

The solubility and dissolution rate of rivaroxaban can be enhanced by the use of SDs of rivaroxaban with PEG 4000. The solubilization effect of used hydrophilic carriers may be contributed due to the reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of rivaroxaban from its SDs. From FTIR spectroscopy, it was concluded that there were no well-defined chemical interactions between rivaroxaban and PEG 4000 in SDs, as no important new peaks could be observed. The DSC study reveals no significant interaction between rivaroxaban and PEG 4000 and there is change in crystallinity of pure rivaroxaban to an amorphous state in their solid dispersions.

ACKNOWLEDGEMENT

The authors would like to acknowledge Royal College of Pharmacy and Health Sciences for providing necessary facilities to carry out the research work.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There is no conflict of interest

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