Original Article

DISSOLUTION RATE ENHANCEMENT AND PHYSICOCHEMICAL CHARACTERIZATION OF RIVAROXABAN SOLID DISPERSIONS WITH POLOXAMER 188

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Abstract

The aim of the work was to enhance the dissolution rate of rivaroxaban by preparing its solid dispersions (SDs) using hydrophilic carrier poloxamer 188. The prepared solid dispersions were characterized by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Both solubility and dissolution rate of the drug in these formulations were increased. The SDs of rivaroxaban with poloxamer 188 were prepared at 1:1, 1:2 and 1:3 w/w ratios by physical mixing, melting and solvent evaporation techniques. The used hydrophilic carrier showed more than two fold increase in dissolution rate in their prepared solid dispersions by melting or solvent evaporation techniques. The FTIR spectroscopic and DCS thermal studies showed the compatibility of rivaroxaban and absence of well-defined drug polymer interactions, though shift in peaks observed due to formation of new bonds.

Keywords: solid dispersions, dissolution rate, poloxamer 188, hydrophilic carrier.

INTRODUCTION

Rivaroxaban is an anticoagulant, factor of Xa inhibitor. It is used as to prevent blood clots. 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 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 there by 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

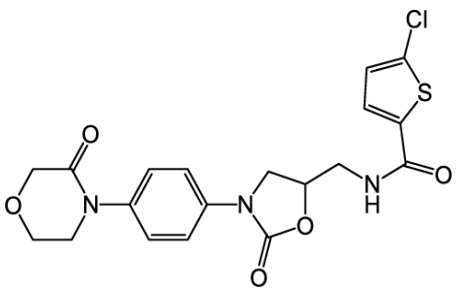

Figure 1: Rivaroxaban

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. 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. Poloxamer 188, poloxamer 407 is 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.4

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.5

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.6

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.7

The primary objective of the present study is to investigate solubility and dissolution rate of solid dispersions of drug in poloxamer 188. 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.8

MATERIALS AND METHODS

MATERIALS

Gift sample of rivaroxaban was received from Dr. Reddy's Laboratories, (Hyderabad, India). Poloxamer 188 was 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 λmax was determined by UV spectrophotometry preparing standard solutions of drug (from 5-40 □g/mL) using acetate buffer pH 4.5 containing 0.5 % w/v SLS. The λmax was found to be 250 nm with a coefficient of determination of 0.999.

Preparation of solid dispersions

The SDs of rivaroxaban with poloxamer 188 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 melting method, the required amount of drug and hydrophilic polymer 188 were melted in a beaker on a heating mantle maintained at a temperature above to a temperature of 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.9

Solvent evaporation

For solvent evaporation the drug and poloxamer 188 were 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 help of heat at low temperature to remove the solvent. The obtained solid dispersions were stored for 48 h in a desiccators containing anhydrous calcium chloride, then scrapped and sieved through a 30-mesh sieve, and stored in a screw-cap vial until further studies.10

Physical mixture

The physical mixtures (PMs) were prepared by thoroughly mixing the required amount of drug with poloxamer 188 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.11

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 ºC. 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 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 ºC, 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.12

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-1.13

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 ºC min-1 from 50 to 300 ºC. An empty aluminum pan was used as reference.14

Table 1: Preparation of SDs with different methods at w/w ratios of poloxamer188.

Polymers used	Drug: Polymer	Method of preparation
Poloxamer 188	1:1 1:2 1:3	PM
Poloxamer 188	1:1 1:2 1:3	SEM
Poloxamer 188	1:1 1:2 1:3	FM

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 concentration range of 5-40 µg/mL, hence follows Beer-Lambert's Law.

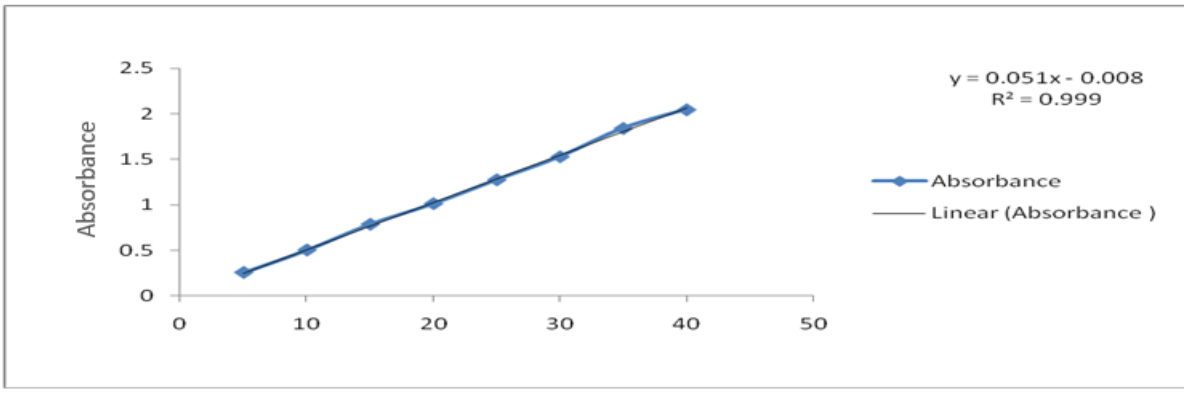

Figure 2: Linear plot of rivaroxaban

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 dissolution of insoluble drugs is the incorporation of a small amount of surfactant in the dissolution medium. The use of surfactants in the 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.

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 dissolution of pure rivaroxaban is very low 37.94 % within 60 min. Solid dispersions of rivaroxaban with poloxamer 188 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 Figure 3. 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, dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and finally, the combination of the above-mentioned methods.

Table 2: Dissolution rate of rivaroxaban

Time (min)	% Drug dissolved
0	0
5	22.65
10	25.58
20	28.45
30	31.40
45	35.86
60	**37.94**

For pure drug dissolution the % drug dissolved was found to be 37.94 % at 60 min.

Solubility enhancement:

Solid dispersions by physical mixing

Table 3: Dissolution rate of rivaroxaban SDs by physical method using poloxamer 188

Time (min)	**% Drug dissolved**		
	1:1	**1:2**	**1:3**
0	0	0	0
5	29.17	30.33	32.45
10	30.17	32.82	34.29
20	32.45	34.97	36.24
30	34.15	37.63	38.74
45	37.27	39.34	42.67
60	45.52	46.65	47.68

In dissolution rate of rivaroxaban SDs by physical method using poloxamer 188 the % drug dissolved was found to be 47.68 % at 60 m.

Table 4: Dissolution rate of rivaroxaban SDs by melting or fusion method using poloxamer 188

Time (min)	**% Drug dissolved**		
	1:1	**1:2**	**1:3**
0	0	0	0
5	39.18	40.71	42.52
10	41.44	43.98	46.56
20	46.67	58.56	54.46
30	53.78	69.45	71.76
45	57.98	81.71	84.43
60	61.41	89.88	90.39

In dissolution rate of rivaroxaban SDs by melting or fusion method using poloxamer 188 the % drug dissolved 188 was found to be nearly 80 % 45 minutes and 90 % after 60 minutes.

Table 5: Dissolution rate of rivaroxaban SDs by solvent evaporation using poloxamer 188

Time (min)	**% Drug dissolved**		
	1:1	**1:2**	**1:3**
0	0	0	0
5	39.78	40.89	41.43
10	41.13	43.37	45.39
20	44.36	49.28	48.62
30	58.45	63.78	69.55

45	62.69	77.59	75.11
60	68.28	88.86	87.56

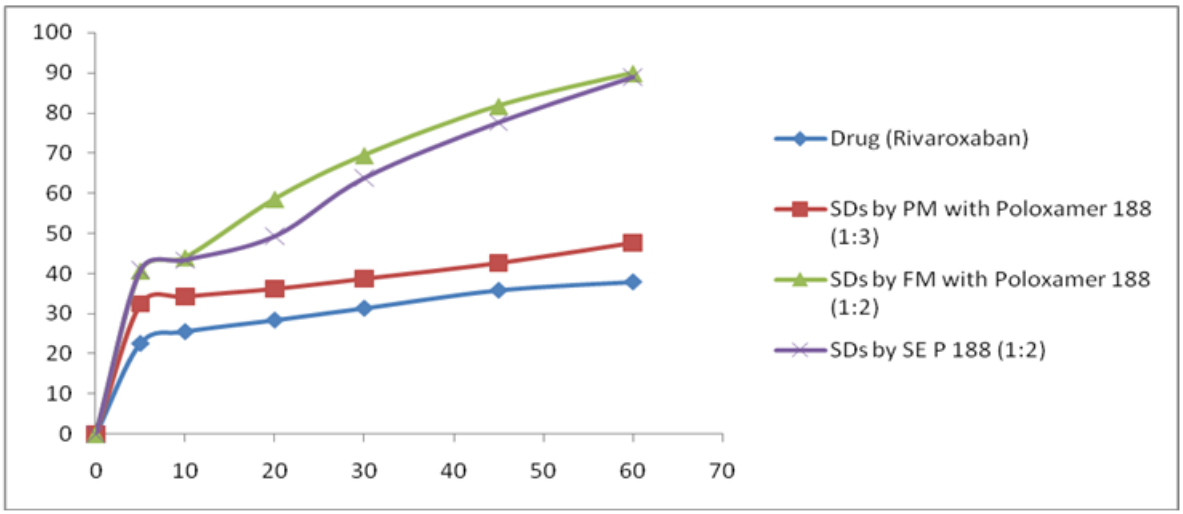

Figure 3: Comparative dissolution rate of optimized SD formulations of rivaroxaban with poloxamer 188 by different techniques

In dissolution rate of rivaroxaban SDs by solvent evaporation using poloxamer 188 % drug dissolved in (1:2) was found to be 88.86 % at 60 m and 77.59% after 45 m

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 aromatic C-H bond. Peak at 2914 cm-1indicates 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 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 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.

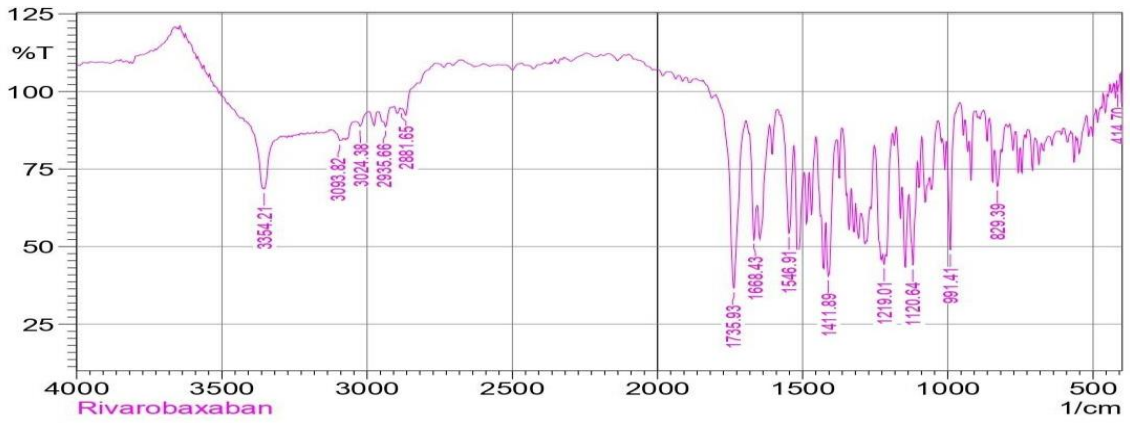

Figure 4: FTIR spectra of rivaroxaban

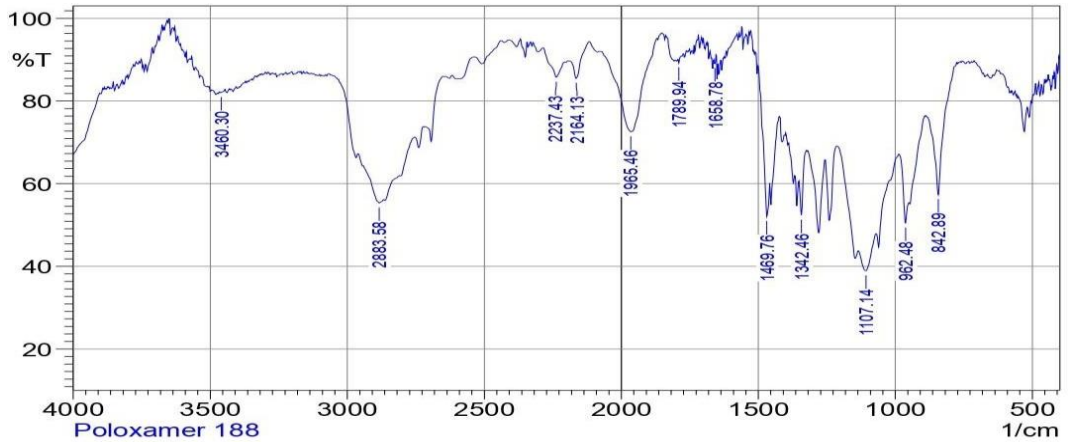

Figure 5: FTIR spectra of poloxamer188

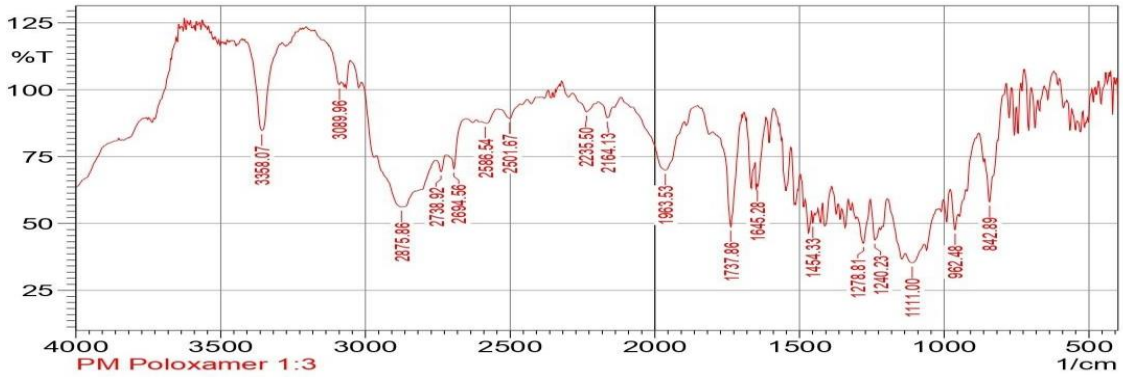

Figure 6: FTIR spectra of physical mixture of rivaroxaban: poloxamer 188 (1:3)

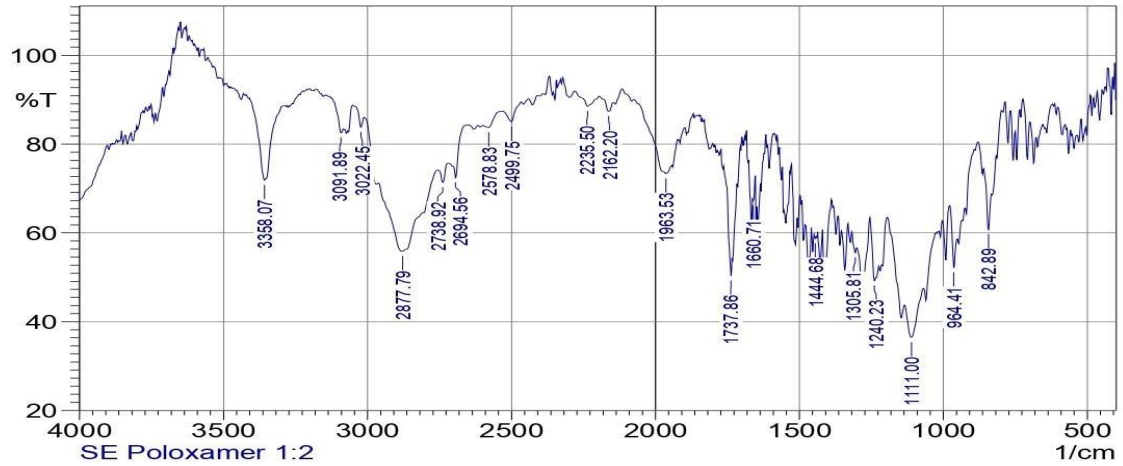

Figure 7: FTIR spectra of solvent evaporation rivaroxaban: poloxamer 188 1:2

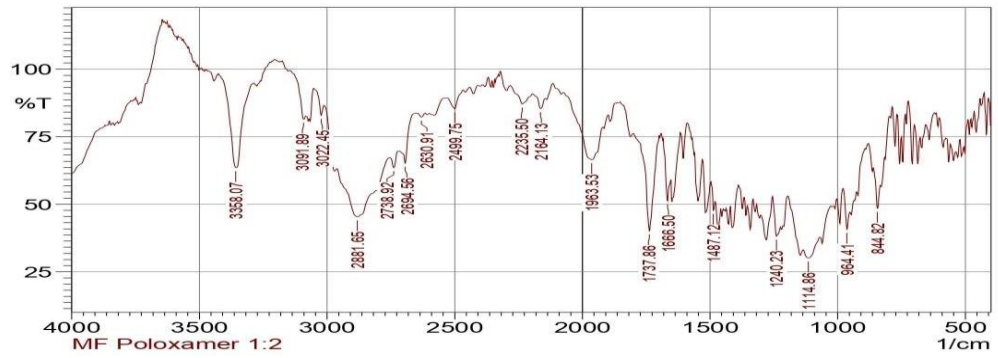

Figure 8: FTIR spectra of solvent evaporation rivaroxaban: poloxamer 188 1:2

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 0C (Remington, 2001). Absence of peak for the drug indicates that the drug is distributed homogenously in an amorphous state with in the solid dispersions without any interactions

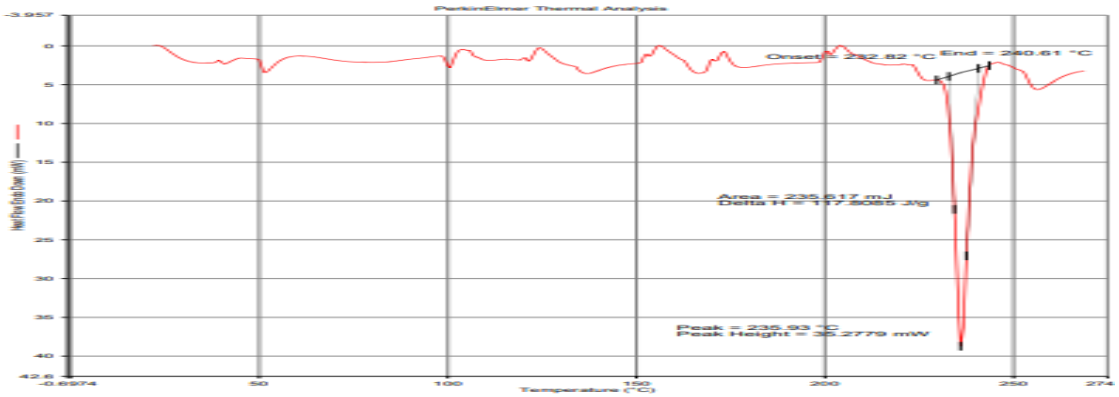

Figure 9: DSC thermogram of rivaroxaban

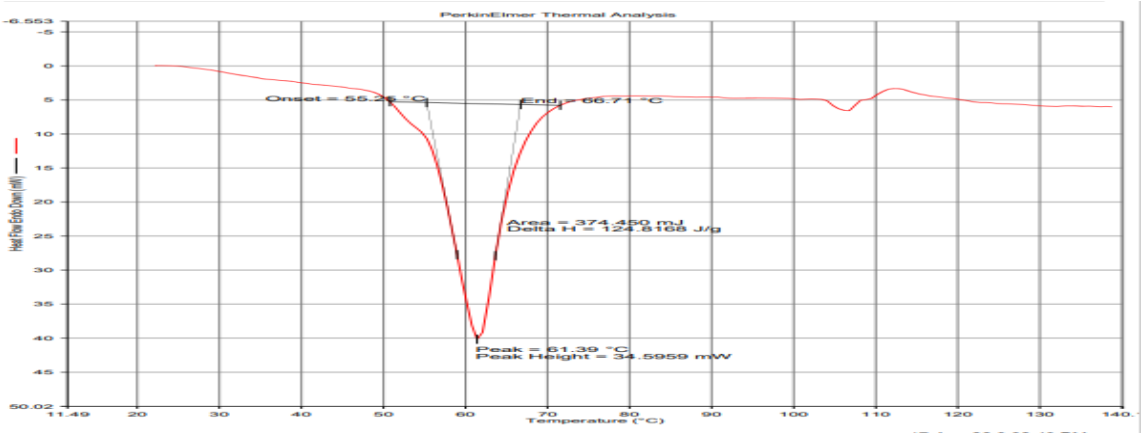

Figure 10: DSC thermogram of Poloxamer 188

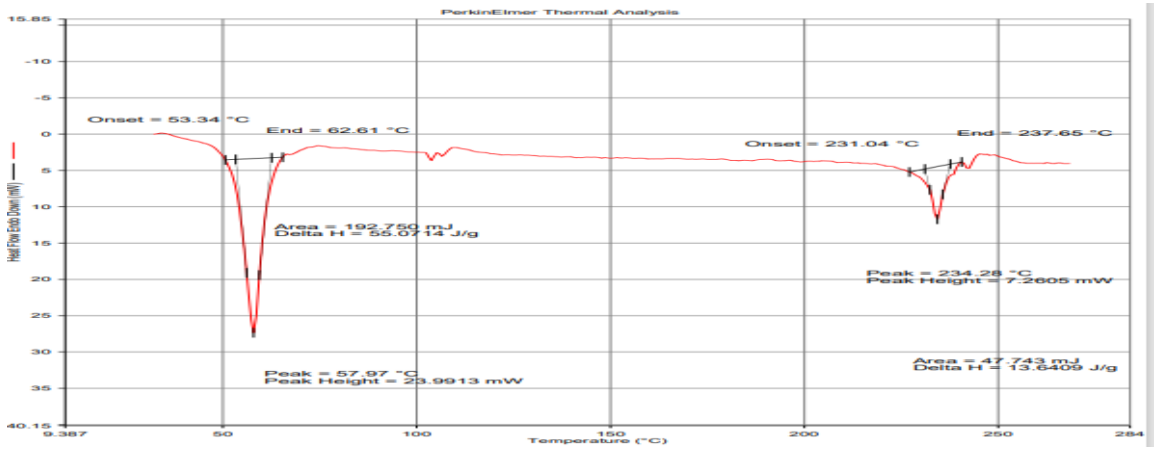

Figure 11: DSC thermogram of poloxamer 188 and rivaroxaban MF

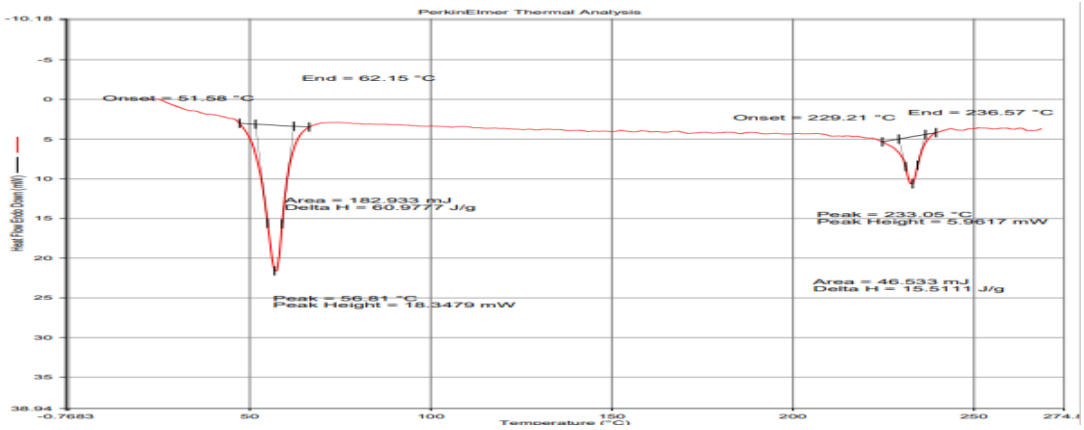

Figure 12: DSC thermogram of poloxamer 188 and rivaroxaban SE

CONCLUSIONS

The solubility and dissolution rate of rivaroxaban can be enhanced by the use of SDs of rivaroxaban with PEG 4000 and poloxamer 188. The solubilization effect of used hydrophilic carriers may be contributed due to 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 or poloxamer 188 in SDs, as no important new peaks could be observed. The DSC study reveals no significant interaction between rivaroxaban and PEG 4000 and Poloxamer 188 and there is change in crystallinity of pure rivaroxaban to amorphous state in their solid dispersions.

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