Original Research Article

RIVAROXABAN: COMPATIBILTY WITH PHARMACEUTICAL EXCIPIENTS USING DSC AND FTIR SPECTROPHOTOMETRY

. **Keywords:** Rivaroxaban, FTIR, DSC, thermal, compatibility, pharmaceutical excipients.

ABSTRACT:

Rivaroxaban (RN) is a recently developed potent oral anticoagulant. The aim of the present study envisages compatibility studies of rivaroxaban with crospovidone, sodium startch glycolate, magnesium stearate, talc, microcrystalline cellulose, aerosil, HPMC K100 M, croscarmellose sodium using Differential scanning calorimeter and FTIR spectrophotometer. DSC thermograms, of rivaroxaban and physical mixture of individual pharmaceutical excipient, exhibited the range of transition of the drug in between 224ºC and 232 ºC. The FTIR graphs showed that the wave numbers of rivaroxaban, matched with all the chosen pharmaceutical excipients combinations. Thus the DSC and FTIR studies showed that RN was not interactive with selected pharmaceutical excipients and can be carried forward for further studies.

INTRODUCTION:

Rivaroxaban (RN) is a potent oral anticoagulant, which was patented in 2007 and approved for medical use in 2011[1]. In 2019, during COVID-19 pandemic situations, it was the most commonly prescribed medication [2]. It is a direct factor Xa inhibitor, used to treat blood clots caused due to various conditions like COVID-19, accidents, hemorrhage etc., Chemically it is (S)-5-chloro-N-((2-oxo-3-(4-(3-oxomorpholino)phenyl)oxazolidin-5yl)methyl)thiophene-2-carboamide[3].

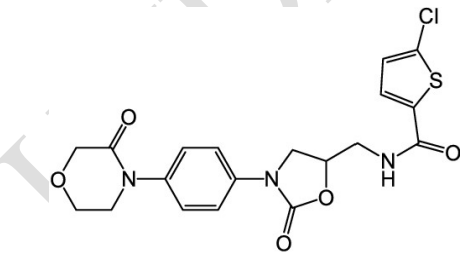

Figure 1: Structure of Rivaroxaban [3]

In view of good demand for RN dosage forms, and to design an effective and stable dosage form, in the present investigation physicochemical incompatibilities of RN with widely employed pharmaceutical excipients was studied.

Drug – excipient compatibility studies is a most important consideration for development of a pharmaceutical dosage form. Interaction of drug with pharmaceutical excipient shall affect physical, chemical, therapeutic properties of drug. In the present paper attempt was made to characterize physicochemical incompatibilities of rivaroxaban with selective widely employed pharmaceutical excipients namely crospovidone (CPN), sodium starch glycolate (SSG), magnesium stearate (MS), aerosil, talc, hydroxypropyl methylcellulose K100M (HPMC K100 M) microcrystalline cellulose (MCC), croscarmellose sodium (CS).

In the present study differential scanning calorimetry and fourier transform infrared spectroscopy were employed to assess physicochemical incompatibilities [4-6]. Differential scanning calorimetry is a thermal analytical technique which provides the temperature of the phase transition of the sample based on the difference of heat required to maintain the same temperature of the reference and the sample pans [7-9]. In DSC, the x-axis is temperature in ºC and on y-axis heat flow in W/g exists. In Fourier Transform Infrared Spectroscopy (FTIR), a graph is plotted with wave number on the x-axis and transmittance on the y-axis, from 4000cm^{-1} to 500 cm^{-1} [10-12].

METHODS:

Materials:

Rivaroxaban was obtained as gift sample from Alfamed Formulations, Hyderabad. crospovidone, sodium starch glycolate, magnesium stearate, aerosil, talc, hydroxypropylmethyl cellulose K100M, microcrystalline cellulose and croscarmellose sodium purchased from Merck were used in the present study.

Instrument:

DSC thermograms were obtained by using DSC, Q20 model of TA instruments with TAQ20 software. FTIR spectra were recorded on a BRUKER alpha model infrared spectrophotometer with OPUS software [8]. Thermal analysis was carried out for RN, RN and physical mixture of RN, selected pharmaceutical excipients (CPN, SSG, MS, Talc, MCC, aerosil, HPMC K100M and CS) in a 1:1 weight/weight ratio. Homogenous physical mixture was weighed to about 2mg directly in the pierced DSC aluminum pan. The sample was equilibrated heated from 30 ºC to 400 ºC at a rate of 10 ºC/min under an atmosphere of dry nitrogen. Here, the term zero air is commonly used for oxygen was used for combustion, thereby increasing the heat as well as temperature and when it reached 300 ºC, the curve is obtained and nitrogen gas cools the sample chamber. FTIR spectra of RN, RN and physical mixture of RN, selected pharmaceutical excipients (CPN, SSG, MS, Talc, MCC, aerosil, HPMC K100M and CS) in a 1:1 weight/weight ratio. These samples were mixed with KBr of IR grade in the ratio of 1:100 and compressed using pellet press. The pellets were then scanned using FTIR spectrophotometer (BRUKER, alpha model) in the range of 4000cm^{-1} to 500 cm^{-1} . The FTIR spectra of physical mixtures were compared with that of the FTIR spectra of pure drug and excipient, to confirm any change occurs or not in the principle peaks of spectra of pure drug and excipient.

Preparation of physical mixtures:

In order to perform the drug-excipient interaction studies, the physical mixtures of 1:1 ratio of the drug rivaroxaban and an excipient was mixed thoroughly using mortar and pestle. These physical mixtures were used for DSC and FTIR studies.

RESULTS:

Thermal behavior of RN, physical mixtures of RN and selected pharmaceutical excipients is illustrated in Figure.2 to Figure. 10. DSC curve exhibited an endothermic peak at 231.88 ºC for RN, corresponding to melting temperature of reference and about similar endothermic peak was exhibited for RN-CPN(224.72 ºC; Figure 3.), RN- SSG(231.75 ºC; Figure. 4), RN-MS(230.17 ºC; Figure.5), RN-aerosil(230.64 ºC; Figure. 6), RN- talc(231.55 ºC; Figure. 7), RN-HPMCK100M(230.64 ºC; Figure.8), RN-CMC(229.75 ºC; Figure.9), and RN-CMS(231.71 ºC; Figure.10). FTIR spectra of RN, physical mixtures of (RN-CPN, RN-SSG, RN-MS, RN-aerosil, RN-talc, RN-HPMCK100M, RN-CMCand RN-CS) are depicted in Figure. 11 to Figure.12). FTIR spectra of pure drug showed characteristic absorption bands located at 3350 cm^{-1} for secondary amide(N-H) stretching, 1730 cm^{-1} corresponding to C-O stretching from the ester group, 1670-1640 cm^{-1} corresponding to amide stretching, 1575-1500 cm^{-1} corresponding to Ar-Cl stretching and N-H scissoring, 1340-1000 cm^{-1} corresponding to C-O-C movement present in both esters and ethers and 850-550 cm^{-1} corresponding to C-Cl stretching respectively. RN showed absorption bands at 3355.33 cm^{-1} for secondary amide (N-H) stretching, 1735.81 cm^{-1} corresponding to C-O stretching from the ester group, 1652.57 cm^{-1} corresponding to amide stretching, 1511.74 cm^{-1} corresponding to Ar-Cl stretching and N-H scissoring, 991.61 cm^{-1} corresponding to C-O-C and 552.96 cm^{-1} corresponding to C-Cl stretching respectively (Figure 13). Similar spectral peaks observed in RN are also observed in all RN- Physical mixtures: RN-CPN(Figure 14), RN-SSG(Figure 15), RN-MS(Figure 16), RN-aerosil (Figure 15), RN-talc (Figure 16), RN-HPMC K100 M (Figure 17), RN-MCC (Figure 18) and RN-CS (Figure 19).

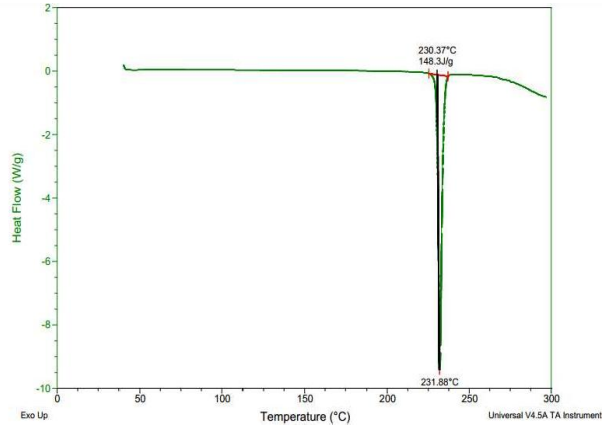

Figure 02: RN

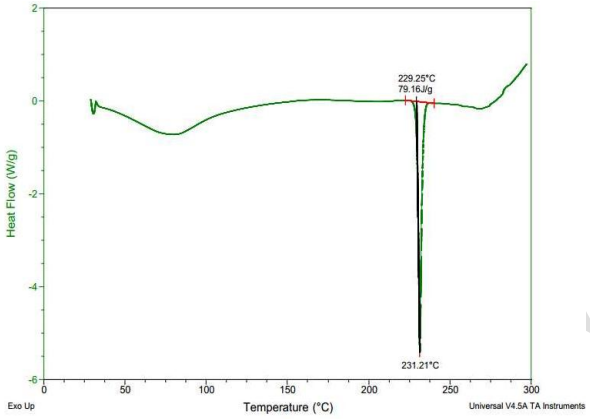

Figure 03: RN+CPN

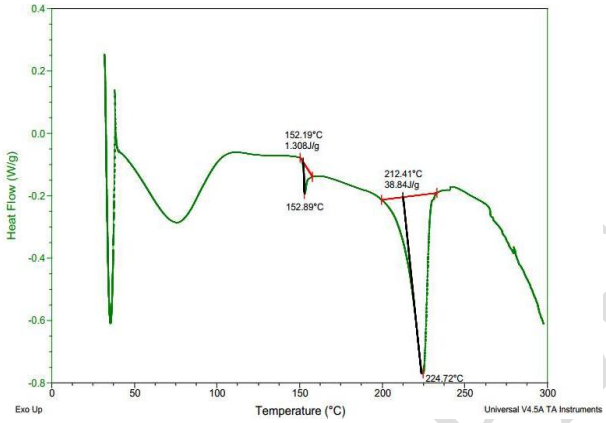

Figure 04: RN+SSG

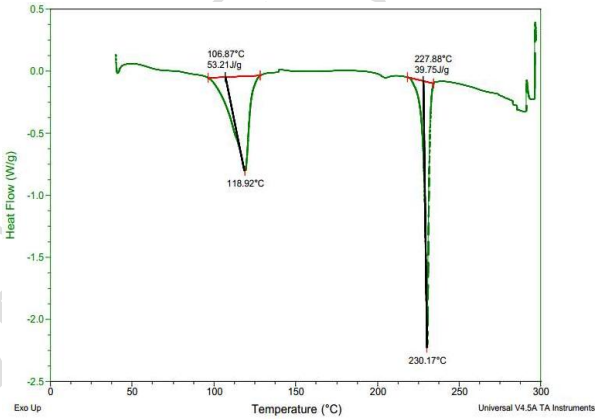

Figure 05: RN+MS

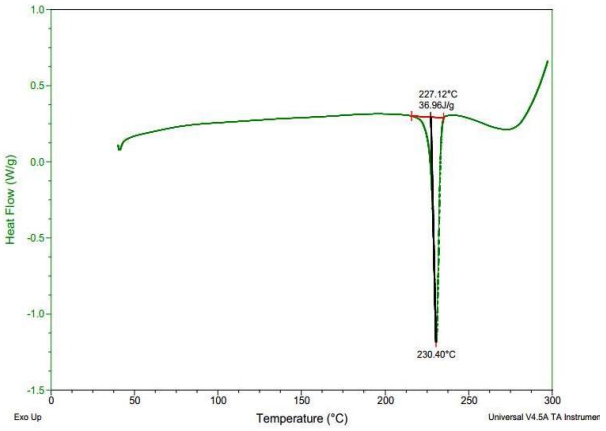

Figure 06: RN+Aerosil

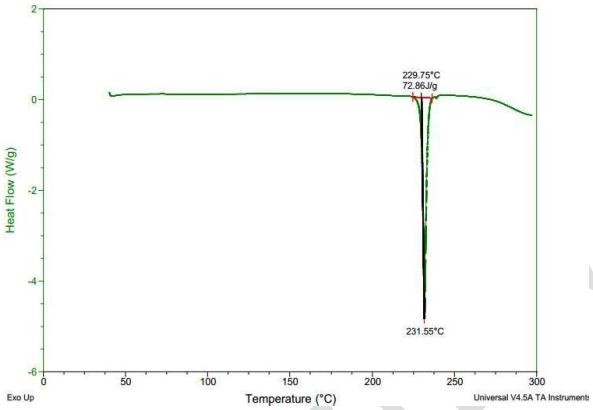

Figure 07: RN+Talc

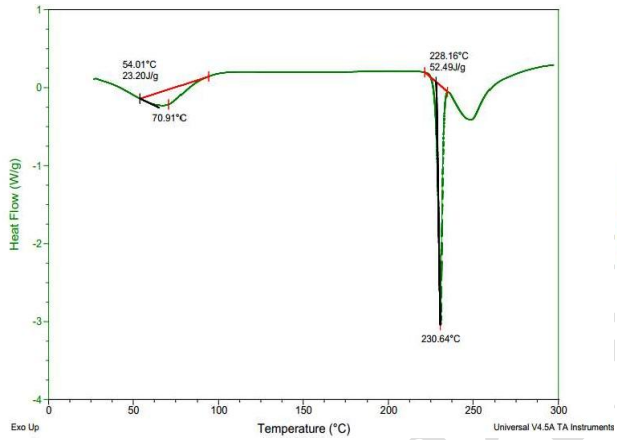

Figure 06: RN+HPMC K100M

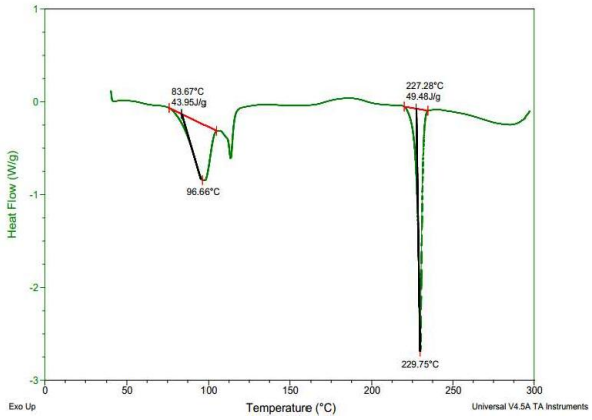

Figure 07 : RN+MCC

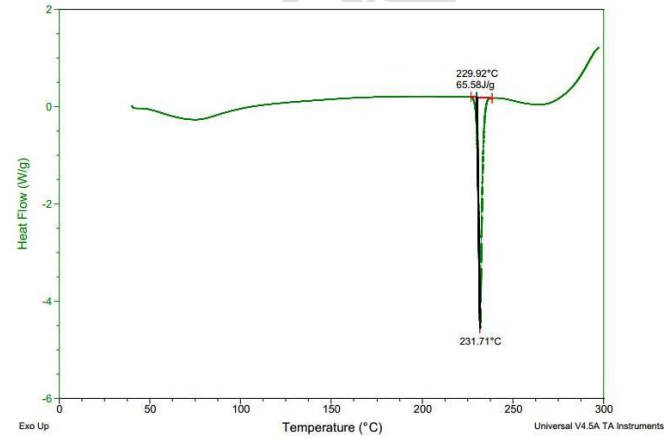

Figure 8: R+CS

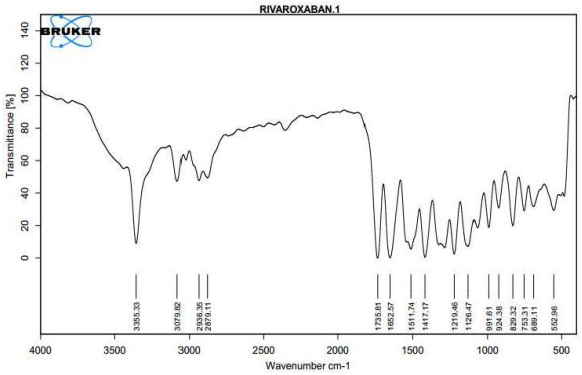

Figure 11: RN

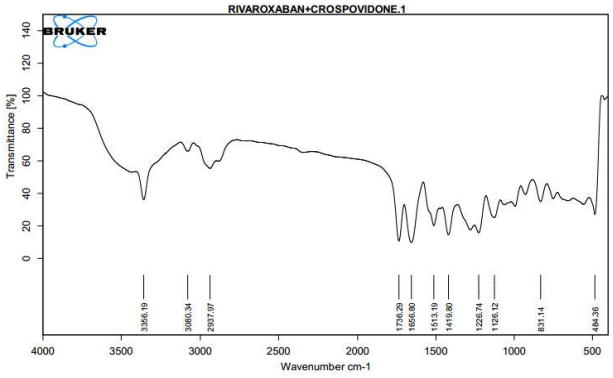

Figure 12: RN+CPN

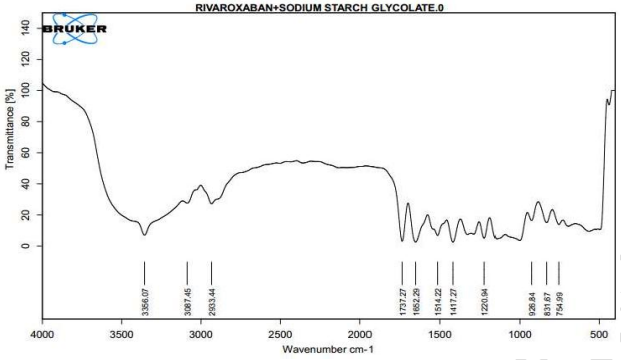

Figure 9: R+SSG

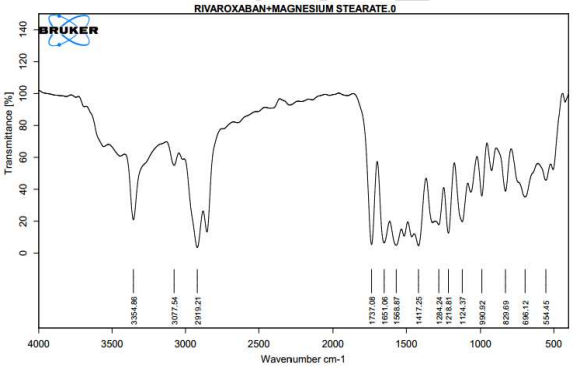

Figure 10: R+MS

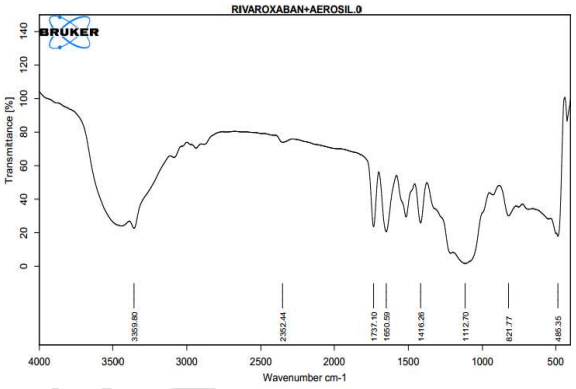

Figure 11: R+Aerosil

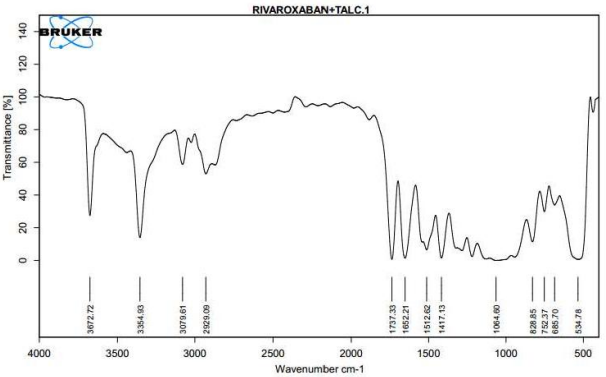

Figure 12: R+Talc

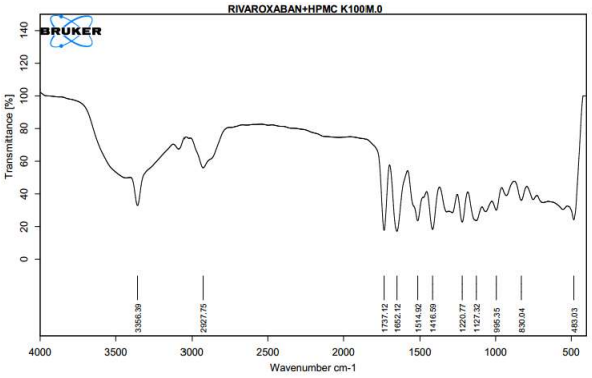

Figure 13: R+HPMC K100M

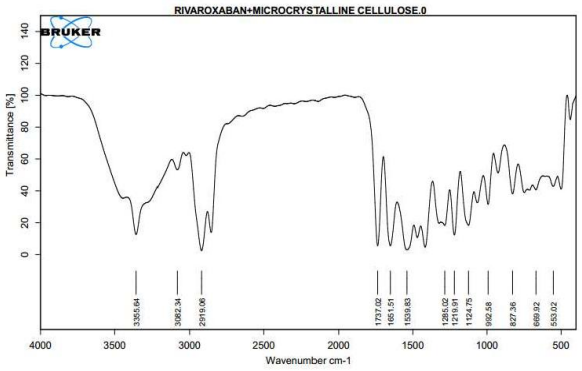

Figure 14: RN+MCC

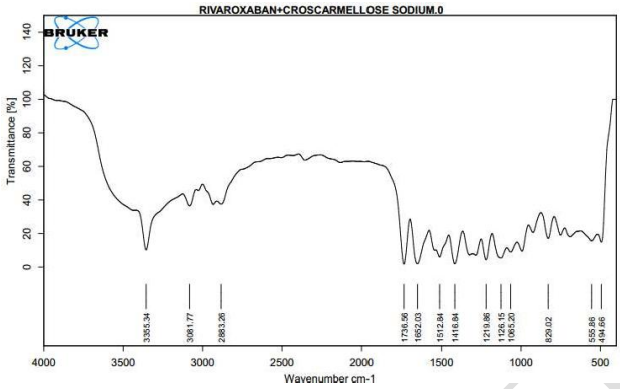

Figure 15: R+CS

DISCCUSION:

The table: 01 shows the heat flow, onset temperatures and peak temperatures of the drug (rivaroxaban) obtained from DSC curves of RN and various drug-excipient physical mixtures. A sharp endothermic peak at 231.88 ºC was observed as the melting point of RN as depicted in Figure: 02. The melting point was observed at 224.72 ºC for RN-CPN, 231.75 ºC for RN-SSG, 230.17 ºC for RN-MS, 230.64 ºC for RN-aerosil, 231.55 ºC for RN-talc, 230. 4 ºC for RN-HPMCK100M, 229.75 ºC for RN-CMC and 231.71 ºC for RN-CMS. Thus the DSC thermogram results confirm that there is no physicochemical interaction between rivaroxaban and selected pharmaceutical excipients of the present study[8-12]. Due to low level of impurities in each component of the physical mixture, minute changes in the melting endothermic peak of RN were observed from 224.72 ºC to 231.75 ºC.

Table 01: Representation of DSC values of all the curves

S.No	Sample	T_{Onset}	T_{Peak}	DH_{fusion}
1.	**Rivaroxaban(RN)**	**230.37** ºC	**231.88** ºC	**148.3 J/g**
2.	Rivaroxaban + Microcrystalline cellulose	227.28 ºC	229.75 ºC	49.48 J/g
3.	Rivaroxaban + Sodium starch glycolate	229.25 ºC	231.75 ºC	79.16 J/g
4.	Rivaroxaban + Crospovidone	212.41 ºC	224.72 ºC	38.84 J/g
5.	Rivaroxaban + Magnesium stearate	227.88 ºC	230.17 ºC	39.45 J/g
6.	Rivaroxaban + Talc	229.75 ºC	231.55 ºC	72.86 J/g
7.	Rivaroxaban + Aerosil	227.12 ºC	230.40 ºC	36.96 J/g
8.	Rivaroxaban + HPMC K100M	228.16 ºC	230.64 ºC	52.49 J/g
9.	Rivaroxaban + Croscarmellose sodium	229.92 ºC	231.71 ºC	65.58 J/g

The common wavenumbers of FTIR graphs in a range 10cm^{-1} are given in Table:01.FTIR spectra of RN showed characteristic absorption bands at 3350 cm^{-1}, 1730 cm^{-1}, 1652.57cm^{-1}, 1511.74 cm^{-1}, 1126.47 cm^{-1} and 552.96 $cm^{-1.}$. FTIR spectral peaks observed in drug substance and physical mixtures were mapped. Thus the absence of any new peaks in the physical mixtures indicated that there are no polymorphic changes in the drug substance during the preparation of physical mixtures. Furthermore, the absence of shifts in the FTIR peaks of the physical mixtures compared to the pure drug indicated the lack of interactions between the drug and polymer components in the physical mixtures at the molecular level[10, 11]. The FTIR studies revealed that there was no chemical interaction between RN and selected pharmaceutical excipients.

CONCLUSION:

Since, the transition temperatures of the drug, rivaroxaban and selected pharmaceutical excipients of the present study were within the limits (DSC thermograms) and also the occurrence of FTIR spectra were similar in case of wave numbers with respect to the drug, it can be stated that there were no possible physicochemical interactions of rivaroxaban and selected pharmaceutical excipients (crospovidone, sodium starch glycolate, magnesium stearate, aerosil, talc, hydroxypropylmethyl cellulose K100M, microcrystalline cellulose and croscarmellose sodium). Results conclude that these combinations are compatible and can be used for further studies, so as to develop pharmaceutical formulations with rivaroxaban.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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