ijlpr 2021; doi 10.22376/ijpbs/lpr.2021.11.3.P25-P32

International Journal of Life science and Pharma Research

ISSN 2250 - 0480

Research Article

Pharma

Physico-Chemical Characterization of Rivaroxaban and Compatibility Studies with Its Pharmaceutical Excipients

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Abstract: Physico-chemical compatibility studies were performed to check the effect of different excipients on API and it is the prerequisite in the preformulation studies. The main aim of this research is to study the behavior of the API individually and with the selected pharmaceutical excipients which mainly contribute in the selection of suitable excipients for developing an ideal dosage form. Rivaroxaban is an oral anticoagulant that mainly acts by blocking coagulant factor Xa. Incompatibility studies were performed for rivaroxaban with selected pharmaceutical excipients like HPMC, lactose, magnesium stearate, sodium lauryl sulfate, microcrystalline cellulose, croscarmellose sodium, HPC using the Scanning electron microscopy, X-ray powder diffraction and differential scanning calorimeter. A 1:1 physical mixture of rivaroxaban and selected excipient was analysed using differential scanning calorimeter. Rivaroxaban showed the transition at 231.79 ^{0}C with 114.2J/g specific heat of fusion. The transition temperature of rivaroxaban has not changed much when compared with the combination of rivaroxaban with excipients. The 2θ values of the standard drug were compared with the spectrum obtained from the XRD study. This comparison showed that there was no evidence regarding the incompatibility of the drug with excipients. The photomicrographs obtained by SEM did not showed any interaction between rivaroxaban and the excipients, providing visual support for the results.

Keywords: Rivaroxaban, Incompatibility, Preformulation, DSC, XRD and SEM

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Recieved On 21 April 2021
Revised On 12 June 2021
Accepted On 24 June 2021
Published On 07 July 2021

Funding The authors are thankful to Chalapathi Institute of Pharmaceutical Sciences and ANI GENERICS, Hyderabad for funding this project.

Citation Rama rao nadendla Satyanarayana Juluri Sai shanmukh srinivas doppalapudi Venkata harshavardhan pyda Avinash tadiboina Vishnuvarddhaan addanki Sai krishna katari Sriharshavardhan kalluri , Physico-Chemical Characterization of Rivaroxaban and Compatibility Studies with Its Pharmaceutical Excipients.(2021).Int. J. Life Sci. Pharma Res.11(4), 25-32 http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.3.P25-P32

1. INTRODUCTION

Incompatibility is the inactivation of a drug through either decomposition or loss of the drug by its conversion to a less favorable physical or chemical form. When we mix two or more API and/or excipients and if they are antagonistic and adversely affect the safety, therapeutic efficacy, appearance, or elegance then they are said to be incompatible. The main aim of this research is to study the behaviour of the individual API and with the mixture of selected pharmaceutical excipients which mainly contribute to the selection of suitable excipients for developing an ideal dosage form by checking the compatibility of API with the excipients by using thermal and microscopical techniques. Rivaroxaban (fig. 1), rivaroxaban is an oral anticoagulant that mainly acts by the mechanism of blocking factor Xa in the mechanism of blood clotting. It belongs to the chemical class of monocarboxylic amide and mainly useful for the prevention and treatment of thromboembolic disorders[1]. The chemical name is 5-Chloro-thiophene-2-carboxylic acid {2-oxo-3-[4-(3-oxo-morpholin-4-yl)-phenyl]-oxazolidin-5-yl}-amide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClNO_5S$ and its molecular weight is 435.9g. Rivaroxaban is slightly soluble in acetone, methanol, acetonitrile, polyethylene glycol 400, and methanol, practically insoluble in water [2-5].

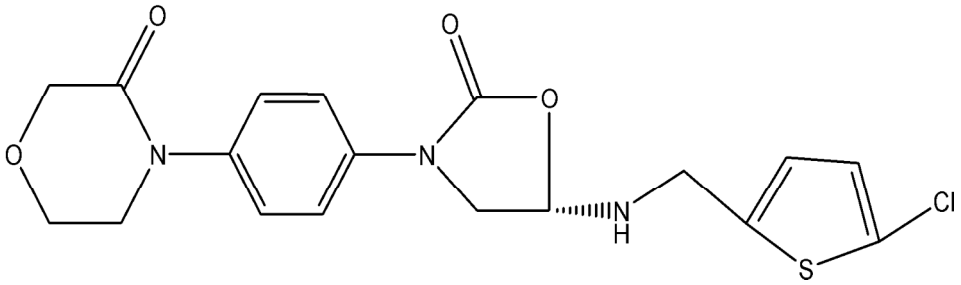

Fig1. Chemical structure of Rivaroxaban

Thermal techniques are used for the analysis of pharmaceuticals and excipients. Different techniques include differential scanning calorimetry (DSC), crystallographic techniques like X-ray diffraction, and scanning electron microscopy (SEM) in which substances are analyzed based on their physical properties reactions with the temperature and are measured by temperature difference [6]. DSC represents a leading thermal analysis technique that has been increasingly used for active pharmaceutical ingredient screening of incompatibilities for over 50 years. In this technique, the DSC curves of pure components are compared with the curves obtained from a 1:1 physical mixture of drug and the excipients. It is assumed that the thermal properties (melting point, change in enthalpy, etc.) of blends are the sum of the individual components if the components are compatible with each other. An absence, a significant shift in the melting of the components, or appearance of a new exo/endothermic peak, and/or variation in the corresponding enthalpies of reaction in the physical mixture indicates incompatibility. However, slight changes in peak shape height and width are expected due to possible differences in the mixture geometry. DSC stands to benefit over other conventional techniques in requirement of the short time of analysis and low sample consumption[7]. In the XRD studies, the samples are checked for the crystalline nature of the compound. The compounds with good crystalline properties tend to have high stability. In XRD, the main principle involved is the diffraction of the rays, when a high beam of incident rays tends to fall on the sample, and the rays get diffracted and this diffraction is measured in terms of angle of deviation. Based on the angle of deviation, comparison between pure API and API with excipients interactions between the components is determined. The formulation development is a significant process in getting to know about the physical and chemical interaction between the substance and excipients[8]. XRD was used in knowing the crystal structure and properties of the molecule and also to know the lattices in the molecule. Scanning electron microscopy is one of the auxiliary techniques to detect incompatibility based on the topographical changes that occur on the particle surface. Here kinetic energy is being applied to produce the signals on interaction with the electrons, these secondary electrons are then backscattered which help detecting the morphology and topography of the sample based on the results obtained from the pictographs, the changes on the particle surface can be assessed and interactions between the drug and excipients can be examined.

2. MATERIALS AND METHODS

2.1 Materials

Rivaroxaban bulk material was procured from Alphamed pharmaceuticals. Hydroxypropyl cellulose, sodium lauryl sulphate were manufactured by S D fine-chem limited Mumbai, India. Magnesium stearate, croscarmellose sodium, and hydroxypropyl methyl cellulose were manufactured by LOBA chemie, Mumbai. Lactose and microcrystalline cellulose were obtained from Merck.

2.2 Instrument

Differential scanning calorimeters manufactured by TA instruments of the Q20 model were used for the studies by using TA instrument explorer and TA universal analysis software under nitrogen atmosphere with the flow rate of 10 mL/min. Approximately 2 mg of samples were weighed and sealed in the aluminum pans. The temperature program was given from 30 to 300°C at a heating rate of 10°C/min[3].X-ray diffraction instrument was manufactured by Bruker(Model - D8). Samples were weighed and placed in a silicon crystal sample holder, placed in the sample position and allowed the X-rays to pass through the sample with an angle ranging from 0 to 80^0. Scanning electron microscope Model ISP, SS300) model was used for SEM analysis. Samples were weighed directly and placed in a pinpoint sample holder and a high intensity beam of electronic radiation was passed through the sample. The pictographs of the samples were taken at different magnifications ranging from 500X to 10,000X.

2.3 Preparation of Physical Mixtures

The study for the interactions was performed by using a

physical mixture of rivaroxaban and excipients of equal proportions (1:1 W/W). The mixtures were prepared by simple mixing using the mortar and pestle, weighed for the required quantity, and were sealed in the aluminium pans for the analysis [9,10].

3. STATISTICAL ANALYSIS

The obtained data of DSC were analysed by using TA instrument explorer and integrated by TA universal analysis software. The obtained results are as followed in table 1

Table 1. Mean transition temperature of rivaroxaban and selected excipients.

S.no	Name of compound	Mean transition temperature ^{0}c	Standard deviation	N (no of trials)
1	Rivaroxaban	231.79	±0.04966	3
2	HPMC	253.40	±0.016	3
3	Sodium lauryl sulphate	185.22	±0.0612	3
4	Magnesium stearate	114.62	±0.08641	3
5	Lactose monohydrate	215.54	±0.0826	3
6	HPC	147.62	±0.114	3
7	Croscarmellose sodium	98.33	±0.239	3
8	Microcrystalline cellulose	242.97	±0.131	3

Standard deviation was calculated for the obtained data by using the software standard Deviation Calculator (version 1.0). The results obtained from the standard deviation were in acceptance criteria (acceptance criteria is ±2^{0}c).

4. RESULTS AND DISCUSSION

4.1 DSC results

The DSC curve obtained for rivaroxaban pure drug is shown in Fig. 2. The DSC curve has shown a sharp endothermic curve at (T_{Peak}=231.79^{0}C; T_{Onset}=230.18^{0}C; DH_{Fusion}=114.2Jg^{-1}), corresponding to melting point followed by decomposition. The DSC data shows evidence that rivaroxaban has thermal stability over 300°C[1,6,9].

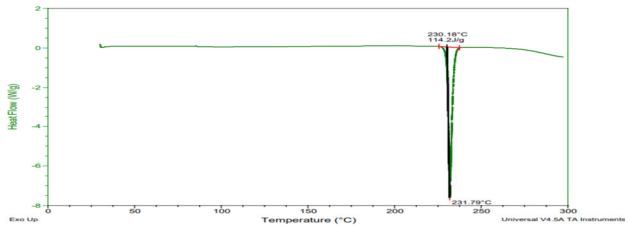

Fig 2. Thermogram of rivaroxaba

DSC has been proposed to be a rapid method for evaluating physico-chemical interactions between the components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and therefore used to select adequate excipients with suitable compatibility[11]. DSC curve of rivaroxaban / HPMC / lactose/ magnesium stearate / sodium lauryl sulphate/ microcrystalline cellulose has shown as an endothermic event of the melting point of rivaroxaban in the range of 226 to 230 ^{0}C, followed by a melting point at 226.10°C. There is a slight decrease in the melting point and heat of fusion of the rivaroxaban when it is being mixed with the combination of excipients. It is acceptable for a small change in the melting points and heat of fusion when a combination of excipients was taken. Finally, the result showed that the absence of movement of the melting drug transition suggests that there were no covalent or other strong interactions with that of its excipients. Hence rivaroxaban was compatible with HPMC/ lactose/magnesium stearate/ sodium lauryl sulphate/ microcrystalline cellulose /HPC/ croscarmellose sodium.

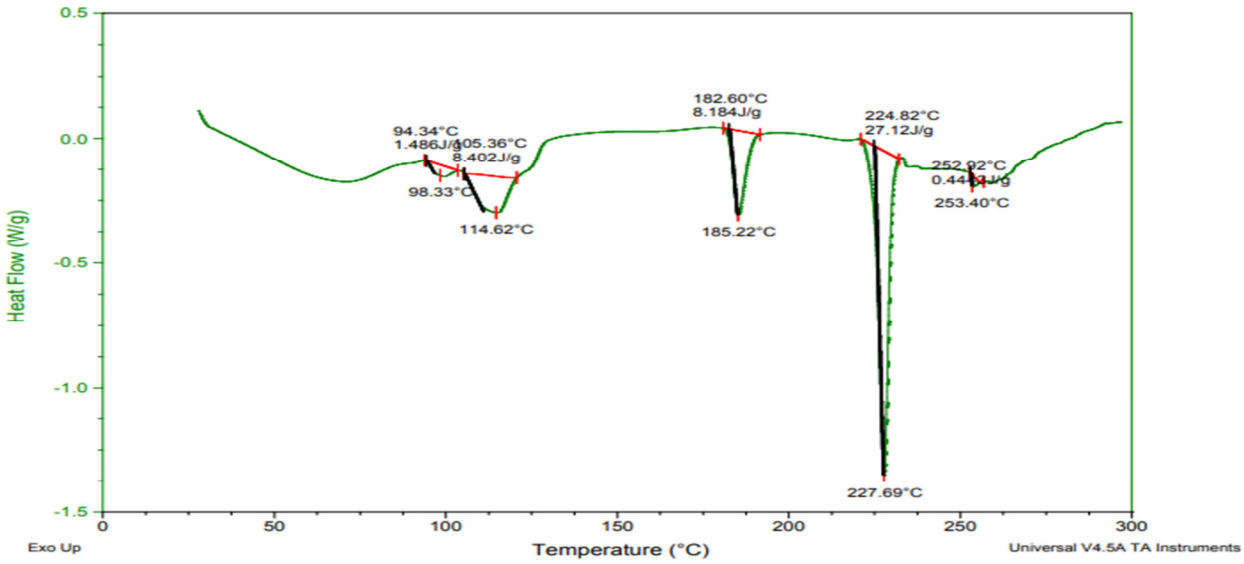

Fig 3: Thermogram of rivaroxaban with its excipients (HPMC/lactose/ magnesium stearate /sodium lauryl sulphate/microcrystalline cellulose/HPC/croscarmellose sodium)

4.2 XRD results

X-ray powder diffraction has been used for qualitative and quantitative identification of crystallinity. The XRD patterns of rivaroxaban revealed several diffraction peaks which indicates its crystalline character. The obtained spectrum is compared with the standard XRD spectrum of rivaroxaban. The standard rivaroxaban XRD spectrum has a diffraction peaks at a 2θ values of 21.84^0, 22.5^0, 25.64^0, 26.64^0 are having more intensive peaks of rivaroxaban, which were considered to be the characteristic peaks of the rivaroxaban [3, 12]. These 2θ values were compared with the diffraction spectrum obtained, where almost all the peaks are retained at the standard 2θ values indicating it is rivaroxaban [13,14].

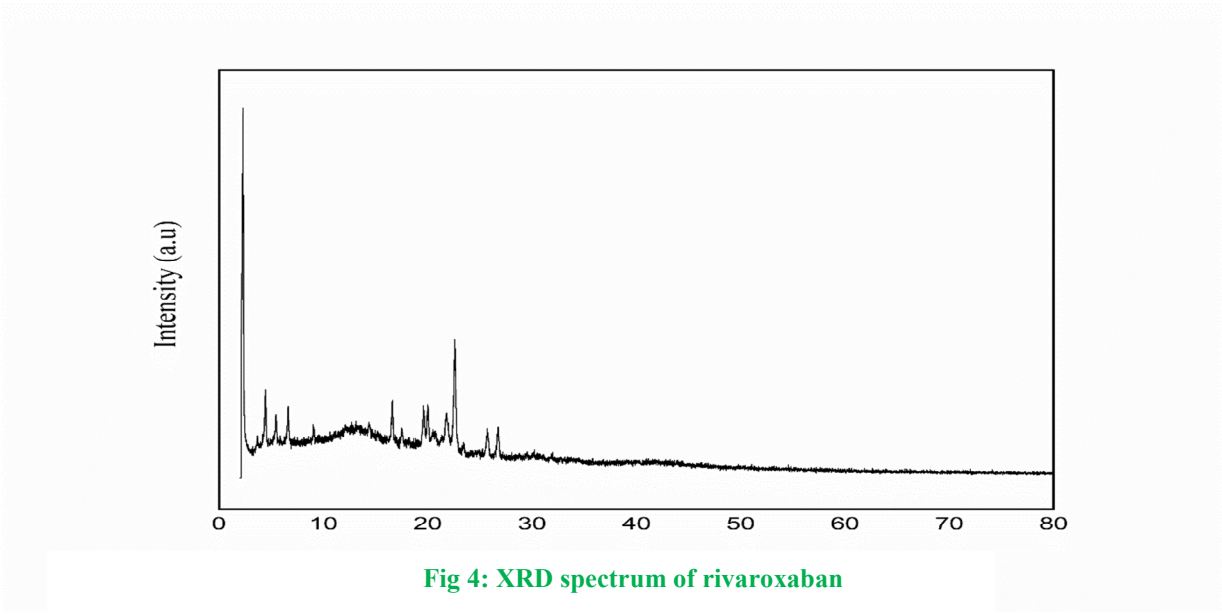

Fig 4: XRD spectrum of rivaroxaban

The standard 2θ values are reciprocated when the mixture of HPMC/lactose/ magnesium stearate /sodium lauryl sulphate/microcrystalline cellulose/HPC/croscarmellose sodium and rivaroxaban are being checked for XRD. There was a slight decline in the intensity of the XRD peaks, however the peaks obtained are at the same angle when it is mixed with the excipients[13]. This shows an indication that rivaroxaban doesn't have any incompatibility with the selected pharmaceutical excipients[15].

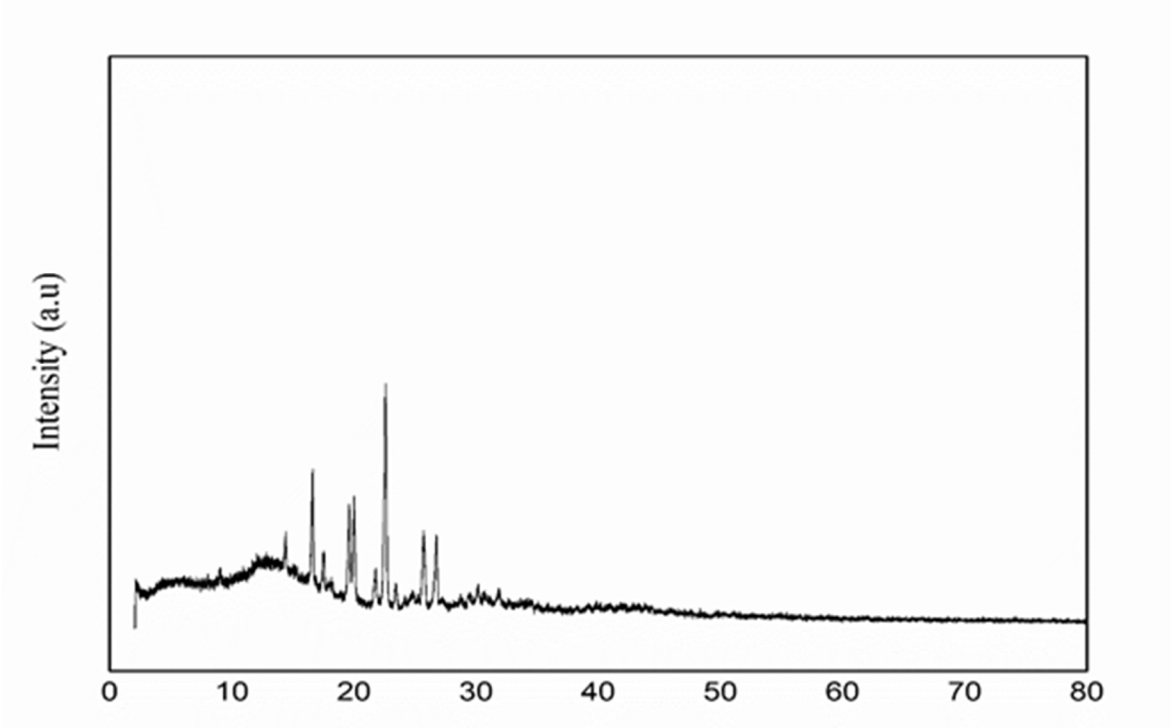

Fig 5: XRD spectrum of rivaroxaban with its excipients (HPMC/lactose/ magnesium stearate /sodium lauryl sulphate /microcrystalline cellulose/HPC/croscarmellose sodium)

4.3 SEM results

The SEM photomicrographs taken at magnification of 500, 1000, 2000, 2500, 5000, and 10,000 were given.(fig 6-11). It was observed that rivaroxaban is characterized by regularly crystals when observed at different magnifications[16]. When the physical mixture is subjected to microscopy the obtained photomicrographs also retained the regular crystal structure of rivaroxaban indicating that the selected excipients were compatible. The photomicrographs obtained by SEM did not evidence any interaction between rivaroxaban and HPMC/ lactose/ magnesium stearate/ sodium lauryl sulphate/ microcrystalline cellulose/ HPC/ croscarmellose sodium, providing visual support for the results[17]. The SEM images have shown that both rivaroxaban and excipient particles maintained their morphology and the drug crystals appeared dispersed on the surface of excipient particles.

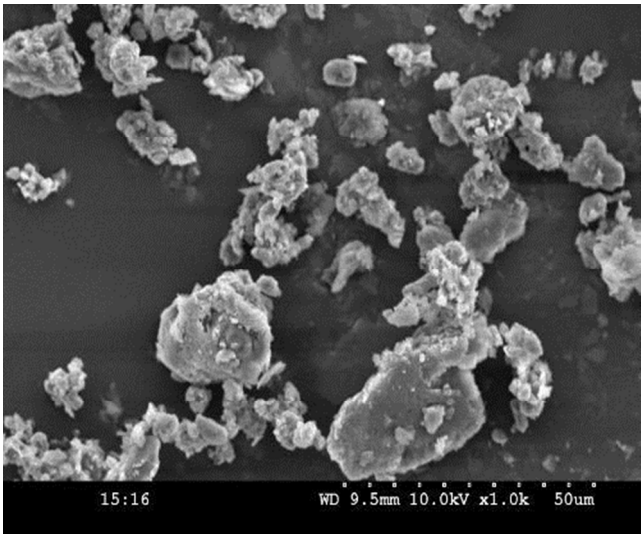

Fig 6: Pictograph of Rivaroxaban at 1000X magnification

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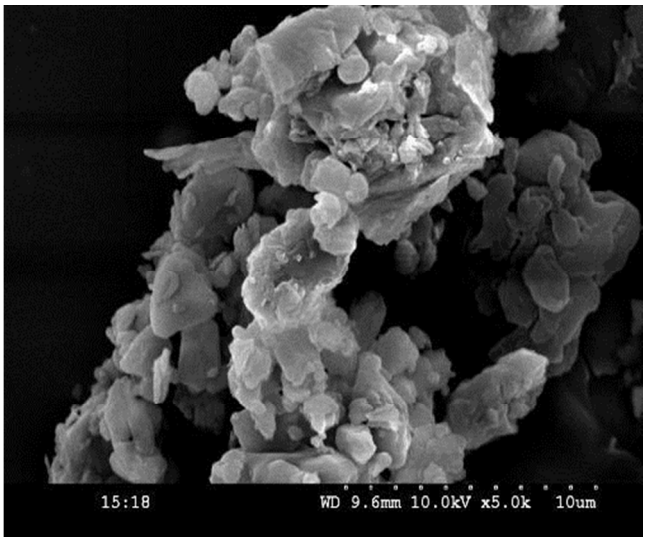

Fig7: Pictograph of Rivaroxaban at 5000X magnification.

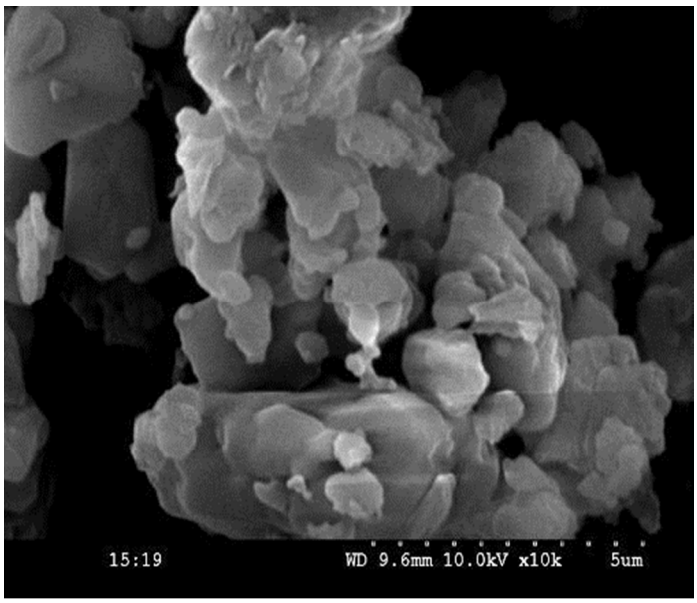

Fig 8: Pictograph of Rivaroxaban at 10,000X magnification

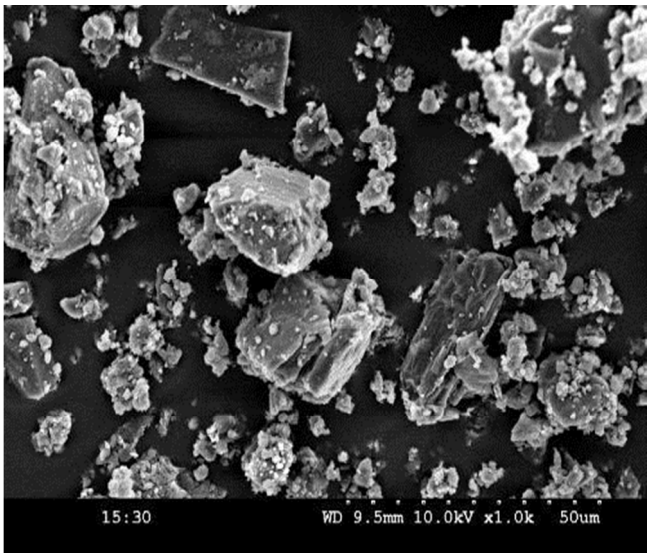

Fig 9: pictograph of rivaroxaban with its excipients(HPMC/ lactose/ magnesium stearate/ sodium laurylsulphate/ microcrystalline cellulose/ HPC/ croscarmellosesodium) at 1000X magnification.

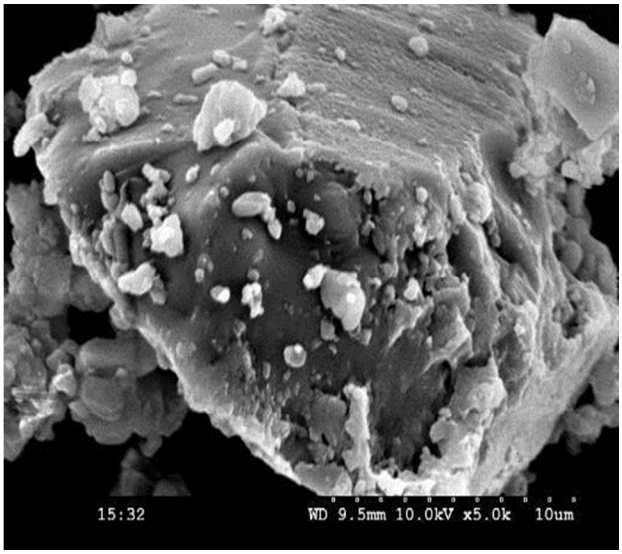

Fig 10: pictograph of rivaroxaban with its excipients HPMC/ lactose/ magnesium stearate/ sodium lauryl (sulphate/ microcrystalline cellulose/ HPC/ croscarmellose sodium) at 5000X magnification

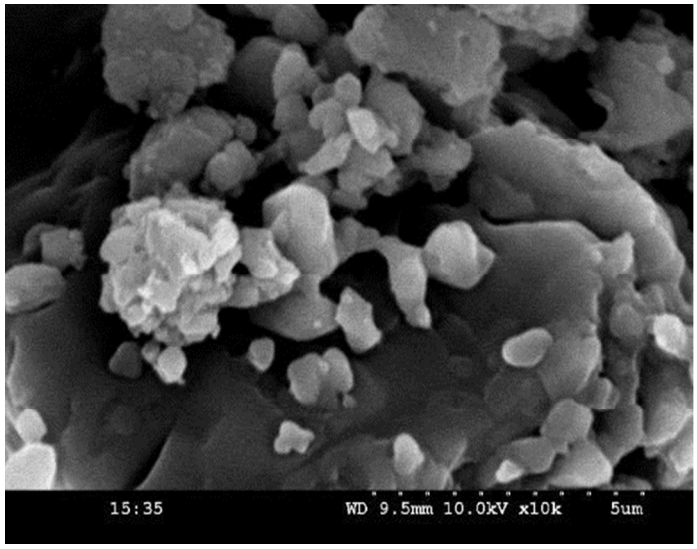

Fig 11: pictograph of rivaroxaban with its excipients (HPMC/ lactose/ magnesium stearate/ sodium lauryl sulphate/ microcrystalline cellulose/ HPC/ croscarmellose sodium) at 10,000X magnification.

5. CONCLUSION

Incompatibility testing has been playing a prominent role in preformulation. Thermal and spectral modes of analysis are key for incompatibility testing. The characterization was obtained by DSC, which, in turn, demonstrated rivaroxaban physicochemical properties including crystallinity. In the compatibility studies, the modifications found in the DSC curves suggested that there was no possible physical interaction of rivaroxaban with magnesium stearate, starch, and microcrystalline cellulose. XRD of rivaroxaban indicated that the compound is crystalline with good diffraction properties. SEM was carried out with rivaroxaban with its excipients and results showed that there were no interactions with good crystal properties from SEM photomicrographs. The thermal analysis provided information about the thermal stability and decomposition of pure rivaroxaban and the binary mixtures which can be used in quality control. These studies play a major role in development of elegant dosage forms. In upcoming prospect, these kinds of studies are helpful in the development of dosage forms with combination of APIs.

6. ABBREVIATIONS

DSC: Differential Scanning Calorimetry

XRD: X-ray Diffraction

SEM: Scanning Electron Microscopy

HPMC: Hydroxypropyl MethylCellulose

HPC: Hydroxypropyl Cellulose

7. AUTHORS CONTRIBUTION STATEMENT

Prof. Ramarao Nadendla conceptualized the work. Satyanarayana Juluri interpreted the DSC data. Complete data was gathered by Sai Shanmukh Srinivas Doppalapudi along with Sai Krishna Katari and Avinash Tadiboina. DSC was performed by Venkata Harshavardhan Pyda. All authors performed the research work and analysed the data with the required inputs towards the completion of the manuscript. All the authors discussed the methodology and results and equally contributed to the final manuscript.

8. ACKNOWLEDGEMENT

The authors are thankful to Chalapathi Drug Testing Laboratory, Chalapathi Institute of Pharmaceutical Sciences, Guntur for accessing all facilities to carry out the research work.

9. FUNDING ACKNOWLEDGEMENT

The authors are thankful to Chalapathi Institute of Pharmaceutical Sciences and ANI GENERICS, Hyderabad for funding this project.

10. CONFLICT OF INTEREST

Conflict of interest declared none.

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