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Enhancement And Optimization Of Dissolution Profiles Of Rivaroxaban Through Dispersed Systems

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ABSTRACT

Background: The solubilization of poorly soluble drugs belonging to Class II of the Biopharmaceutical Classification System (BCS) is often a challenge in screening studies of new chemical substances as well as in formulation design and development. One of the most difficult aspects of formulation design is the Solubility properties. A number of methods can be used to improve the solubilization of poorly water-soluble drugs and further improve their bioavailability. Rivaroxaban, an anticoagulant, is classified as a poorly soluble BCS class II drug. Solid dispersion technologies provide promising results for improving the oral absorption and bioavailability of BCS class II drugs. The present study highlights the critical role of particle size reduction and increased surface area in improving the solubility, dissolution rate and subsequent bioavailability of rivaroxaban.

Results: Incorporation of solid dispersions containing linear polymers further enhances these effects by creating larger, more porous particles that accelerate drug release. The strategic combination of HPMC and SLS in one formulation synergistically addresses the challenges associated with poorly soluble drugs. HPMC acts as a matrix former, facilitating the formation of a hydrogel layer around the drug particles and complementing the wetting agents of SLS that break down dissolution barriers. Consequently, the joint inclusion of HPMC and SLS not only exceeds the individual contributions of each component but also ensures improved therapeutic efficacy through improved drug release and absorption. The finer particle size formulation resulted in a higher dissolution rate of 100% after 30 minutes, likely due to the larger surface area of the smaller particles, resulting in faster drug release and improved bioavailability. Furthermore, the amorphous state of rivaroxaban proves to be a key factor in enhancing drug release by eliminating the energy barrier associated with the dissolution of the crystal lattice.

Conclusion: This innovative strategy holds promise for the advancement of pharmaceutical technology and enables the development of more effective drug formulations that overcome the limitations of poorly soluble drugs, thereby leading to better therapeutic outcomes for patients. The present study offers remarkable potential for revolutionizing drug delivery systems and ushers in the era of innovative medicines characterized by increased therapeutic efficacy, improved patient adherence and improved overall health outcomes..

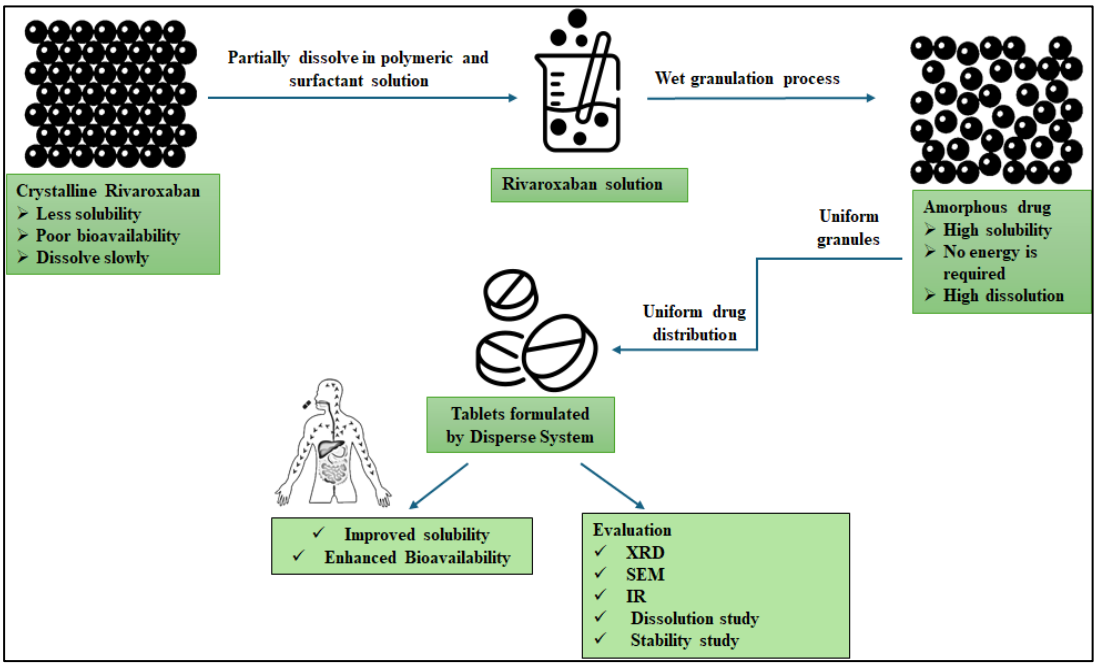
Keywords: *rivaroxaban, solid dispersion, particle size, surface area, solubility, dissolution rate, bioavailability*

1. INTRODUCTION

Recent discoveries of drugs with low water solubility have posed challenges to pharmaceutical formulation scientists as they may limit oral bioavailability (Bhamare et al., 2021). Improving the solubility of these drugs is crucial for the screening of new chemical entities as well as for the design and development of formulations. There are various methods to improve their solubility, resulting in increased bioavailability (Albetawi et al., 2021). For optimal absorption, drugs must be present as aqueous solutions at the absorption site. In vivo absorption is influenced by solubility and permeability, which can be altered by amplification techniques. Poorly soluble compounds falling under Class 2 of the Biopharmaceutics Classification System (BCS) pose significant formulation challenges, limit delivery technologies, and complicate dissolution testing, often resulting

in poor correlation with in vivo absorption. Oral formulations determine drug effectiveness by dissolving drugs in the digestive system before they are absorbed through the small intestinal membrane. Techniques vary depending on the BCS class, solubility and membrane permeability of the drug. Class II fractions with low solubility and high permeability have high absorption but low dissolution, making dissolution the rate-limiting step (Kasturi & Malviya, 2021).

GRAPHICAL ABSTRACT



Highlights

- Formulation F2, which uses a solid dispersion, showed rapid drug release and reached a 100% Q value in 30 minutes, surpassing the Innovator's 95.7% value.
- The FT-IR spectrum of F2 revealed no interaction between the excipients and rivaroxaban, confirming its chemical stability.
- The drug remained in an amorphous state in F2, ensuring product performance.

The tablet formulation F2 maintained structural integrity and high dissolution rates, confirming its stability under both real-time and accelerated conditions

Solubility is crucial for drug release, absorption and oral bioavailability. Most new drugs have low water solubility, making them difficult to formulate into delivery systems. Improving solubility is a necessary preformulation phase in pharmaceutical product development research (Tambosi et al., 2018). Bioavailability can be improved by increasing the solubility and dissolution rate of the drug in gastrointestinal fluids, particularly for BCS Class II compounds. The primary limitation to the absorption of BCS Class II drugs is their release from the dosage form and their Solubility in gastric secretions, not the absorption process itself. Therefore, increasing solubility directly correlates with increased bioavailability of BCS class II drugs (Sharma et al., 2019).

Rivaroxaban, an oral anticoagulant, is used to treat and prevent deep vein thrombosis and pulmonary embolism by inhibiting factor Xa. It is classified as a Class II poorly soluble drug in the BCS system (Karakucuk, 2020). Improving the oral bioavailability of poorly soluble drugs is challenging due to their poor solubility and low dissolution rate in aqueous gastrointestinal fluids and requires careful formulation designs for consistent bioavailability. Solid dispersion technologies have been proven to improve the solubility of poorly water-soluble drugs, particularly those classified as BCS Class II. These methods are selected based on factors such as the properties of the drug, the excipients chosen and the dosage form (Nikam et al., 2020). In addition, changes in the molecular structure of a drug can also increase its solubility. Solid dispersions are the most attractive method for increasing the bioavailability of poorly water-soluble drugs. Solubilization is the process of increasing the visible solubility of a substance that is poorly soluble in water (Bertoni et al., 2020).

Solid dispersion formulations offer a range of processing options and excipients, providing greater flexibility in formulating oral delivery systems for these drugs. Conversion of the drug to an amorphous state within these formulations can increase its solubility and bioavailability (Feng et al., 2018). Approaches include particle size reduction, polymorphism, surfactant application, and solid dispersion. These physicochemical approaches aim to improve the oral absorption of drugs with poor

water solubility (Schittny et al., 2020).

Particle size reduction is a promising method to improve the bioavailability of lipophilic drugs by increasing surface area and saturation solubility by reducing particle size to submicron levels. This process results in an expanded contact area between solubilized molecules and a solvent, which directly affects the solubility, dissolution rate, and extent of absorption (Kumar et al., 2021). Particle size is crucial in preformulation research because it is related to the bioavailability of poorly soluble drugs. By reducing particle size, greater surface area can be achieved, enabling a wider range of formulation techniques and delivery technologies. This larger surface area intensifies interactions with the solvent and thereby increases solubility (Dizaj et al., 2015).

Drugs have crystal forms with different solubility. Amorphous materials are more soluble and dissolve faster than crystalline materials due to their lower binding energy. Solid dispersion technologies can improve the oral absorption and bioavailability of BCS class II drugs (Bhalani et al., 2022). The choice of method depends on the physicochemical properties of the drug, carrier properties and intended applications. Elimination of crystalline structure and molecular dispersion in a hydrophilic polymer support improves solubility (T. T. D. Tran & Tran, 2020). The amorphous state has a relatively high free energy, resulting in increased water solubility and oral absorption (Pandi et al., 2020). Solid dispersions are formulations that use a hydrophobic active ingredient dispersed in a hydrophilic carrier, resulting in increased surface area and improved solubility. These formulations can be improved by using the drug in its amorphous state, which requires less energy to break the crystal lattice when dissolved. Carriers in solid dispersions are divided into three different classes: first, second and third (P. Tran et al., 2019).

This current study discusses the use of surfactants in the preparation of solid dispersions that improve the solubility and bioavailability of water-soluble drugs. Surfactants can alter the hydrophobicity of drugs, reduce surface tension, and serve as wetting agents, detergents, emulsifiers, foaming agents, and dispersants (Han et al., 2021). The optimal carrier should increase the solubility and dissolution, reduce the particle size, and ensure physical stability (Nair et al., 2020). The properties and concentration of the polymer of a formulation also affect the dissolution profile of a solid dispersion drug (Budiman et al., 2023).

Surfactants in solid dispersions increase the dissolution rate and physical stability of poorly water-soluble compounds (Chaudhari & Dugar, 2017). They reduce the interfacial energy barrier between the drug and the dissolution medium, thereby enabling improved wettability (Bolourchian & Panah, 2022). Surfactant concentrations above the critical micelle concentration (CMC) improve drug solubility and result in faster dissolution rates. When exposed to aqueous solutions, the carrier dissolves, releasing the drug in the form of fine colloidal particles and increasing the surface area, dissolution rate and bioavailability of poorly water-soluble drugs. Changing the drug release profile can improve bioavailability by reducing particle size and increasing porosity (Sharma et al., 2019). Surfactants in pharmaceutical technology help to economically dissolve soluble substances by increasing the hydrophobicity and electrical charge of the particles. They serve as carriers, dispersants and emulsifiers, enhancing drug-solvent contact and providing increased solubility and rapid molecular dissolution (Muhammad Suhail et al., 2019).

When solid dispersions are produced, a layer of active ingredient forms on the surface, which prevents dissolution and prolongs the release of the active ingredient. The dissolution rate of a component in a multicomponent mixture can be influenced by another component and the choice of carrier (Chaudhari & Dugar, 2017). A water-soluble carrier accelerates drug release from the matrix, whereas poorly soluble or insoluble carriers slow it down. A faster release of active ingredient can be achieved if the active ingredient is a smaller component of the dispersion (Nair et al., 2020). This research study investigates the synergistic effect of combining surfactants with polymers in solid dispersions and explains how this combination increases the dissolution rate of the drug

2. METHODS

Materials used

Rivaroxaban pure drug obtained from Moehs Eberica, Spain, lactose monohydrate (DMV Fonterra), microcrystalline cellulose 101 (FMC biopolymer), cross-selling sodium (FMC biopolymer), hydroxypropyl methylcellulose (BASF), sodium lauryl sulfate (BASF) and magnesium stearate (Peter Greven) were used. All the materials used were of analytical grade.

API Intrinsic solubility dissolution

20 mg of Rivaroxaban API powder was accurately weighed and added into the dissolution medium. For this study, six different active pharmaceutical ingredients (APIs) were purchased from six different manufacturers. The goal is to test their inherent solubility, taking into account the differences in particle size between them. The test was performed using a USP Type II paddle apparatus set at 75 rpm in 900 ml of acetate buffer, pH 4.5, supplemented with 0.4% sodium dodecyl sulfate as dissolution medium. The temperature was maintained at 37 ± 0.5 °C. The samples were then analyzed using HPLC and the results were documented. The method developed in the present study was adapted using the USP monograph with minor modifications (Meng et al., 2022).

Selection of the active polymorphism and particle size

The active pharmaceutical ingredient (API) rivaroxaban was purchased from the manufacturer in Moehs, Spain. This study was conducted to determine the particle size distribution (PSD) of rivaroxaban in the innovator's product, the reference drug product (RLD), and the API using hot stage microscopy. The tablet formulation used a reverse engineering approach to analyze and select polymorphic shapes and particle sizes of the purchased active ingredient. This process ensures that the particle size of the captured active ingredient matches that of the RLD, ensuring consistency and quality in tablet preparation. The method developed by Bolourchia & Panah 2022 was adapted with minor modifications in the present study (Bolourchian & Panah, 2022).

i. Tablet preparation

The raw material was passed through a 20 mesh size and mixed in a high speed mixer granulator (RMG). API was dispersed in solutions of hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulfate (SLS), and the binder solution was kneaded until granules were formed. Wet granules were dried, sieved and classified. Oversized granules were crushed in a Fitz mill and mixed with magnesium stearate. The finished powder was pressed into tablets, which were then coated with a dark red color.

The anticoagulant tablet formulation includes both intragranular and extragranular phases as well as a coating to improve dissolution and overall functionality. In the intragranular phase, lactose monohydrate is used as a diluent/filler, accounting for 26.94% of the total core weight, to add bulk to the tablet. In addition, microcrystalline cellulose at 41.18% serves as a further diluent and helps to improve the compressibility and mechanical strength of the tablet. Croscarmellose sodium (3.53%) acts as a disintegrating agent, making it easier to break the tablet after ingestion, resulting in faster dissolution. The binder preparation contained rivaroxaban, the active anticoagulant, which constituted 23.53% of the core weight of the tablet. To ensure the integrity of the tablet, HPMC was used as a binder (3.53%), while sodium lauryl sulfate (0.59%) served as a solubilizer to increase the dissolution rate of rivaroxaban. In the extragranular phase, magnesium stearate (0.71%) is added as a lubricant to prevent the ingredients from sticking to the tablet press during manufacturing. The total core weight of the tablet is 100%. Additionally, the tablet is coated with Opadry Dark Red (2.94%), which acts as a coating material, increasing the total weight of the tablet to 102.94%. This coating improved the appearance of the tablet, provided protection from moisture and controlled the release of the active ingredient.

ii. Sample preparation

The tablet contents were dispersed in water (approximately 1:5 w/v ratio) and vortexed for 2 minutes to dissolve the soluble contents in water. The mixture was then centrifuged at 5000 rpm for 1 minute. The supernatant containing soluble components was discarded. A sample of the sediment was mounted on a glass slide and observed under a microscope for particle size analysis. API and RLD underwent similar sample preparation and analysis.

iii. Stage microscopy

Using an optical/polarized hot stage microscope (Leica DMLP, Leica, Germany) with a controlled heating and cooling stage (LTS350, Linkam) and an imaging system (VTO 232, JVC - digital camera and Linksys 32 imaging software, Linkam, England), the particle size of the API in the tablets was measured using a pre-calibrated benchtop micrometer. A small amount of the sample was placed on a microscope slide and examined under a microscope. The sample was examined at a minimum size of 3.5 micrometers at 500x magnification.

Polymorphism determination via X-ray diffraction (XRD)

Lattice spacing was measured using XDC-700 (Stockholm, Sweden) using XRD with a Guinier camera. A tiny sample was placed in a rotating holder and exposed to CuKa radiation (151.540598 Å) at 40 kV and 320 mA. The X-ray generator, a PW-Solution 1720 (Philips-Eindhoven, Netherlands), was equipped with a crystal monochromator. At room temperature, direct beam exposure was maintained at 10 kV and 5 mA for 2 s throughout the experiment. The Fouad et al. Method 2021 developed was adapted with minor changes in the present study (Fouad et al., 2021).

Scanning electron microscopy (SEM)

SEM analysis was performed using a Philips XL-30 SEM (Basel, Netherlands). The samples were coated with 20 nm gold before examination using the SEM Gold Sputtering System 6 to ensure an electrically conductive surface (Anwer et al., 2020).

Preparation of Rivaroxaban Tablets via Optimized Solid Dispersion

Various formulation components of rivaroxaban immediate-release tablets (F1 to F5) were prepared at different concentrations. The raw material was passed through a 20 mesh sieve to remove the foreign matter and put into RMG for the dry mixing process. The API was dispersed in HPMC and SLS solutions and stirred continuously until a homogenized solution was formed. The binder solution was poured into the RMG and then kneaded until good granules were formed. The wet granules were dried using a fluidized bed dryer and then sieved through a sieve 20 to separate the granules that were too

small and those that were too large. The oversized granules were passed through a Fitz mill to reduce the size of the granules and mixed well with magnesium stearate. The finished powder was pressed into a tablet that was coated with a dark red color (Inc, 2024).

Formulation Trials

Table 1: Formulation Trials

Process	Ingredients	F1	F2	F3	F4	F5
		mg/tab	mg/tab	mg/tab	Mg/tab	mg/tab
Intragranular	Lactose monohydrate	22.90	30.00	29.98	29.98	45.00
	Microcrystalline cellulose	35.00	60.00	60.00	58.80	45.00
	Croscarmellose sodium	3.00	4.20	4.23	4.23	4.21
Binder preparation	Rivaroxaban	20.00	20.00	20.00	20.00	20.00
	Hydroxypropyl methyl cellulose	3.00	3.60	4.23	5.43	4.23
	Sodium lauryl sulfate	0.50	1.20	0.71	0.71	0.71
	Purified water	QS	QS	QS	QS	QS
Extragranular	Magnesium stearate	0.60	1.00	0.85	0.85	0.85
	Core Tablet Weight	**85.00**	**120.00**	**120.00**	**120.00**	**120.00**
Coating	Opadry II Dark red	2.50	3.60	3.60	3.60	3.60
	Purified Water	QS	QS	QS	QS	QS
	Total Weight of Tablet	**87.50**	**123.60**	**123.60**	**123.60**	**123.60**

In vitro Dissolution Profile

Dissolution experiments were carried out using a United States Pharmacopeia (USP) Type II dissolution apparatus and a USP monograph at 75 rpm and 37 ± 0.5 °C with 900 ml of acetate buffer, pH 4.5 (containing 0. 4% sodium dodecyl sulfate), carried out the dissolution medium. At appropriate intervals of 0, 5, 10, 15, 30, 45 and 60 minutes, samples were removed and their volume replaced with an equal volume of dissolution medium. After filtering, the samples were diluted. The sample was analyzed using high performance liquid chromatography (HPLC) and tested using the protocol listed below (Patra et al., 2022).

Release and shelf life limit:

At least 80% (Q) of the labeled amount of rivaroxaban was dissolved in 30 minutes.

HPLC conditions:

Chromatographic conditions included a Waters Spherisorb ODS2 column (4.0 × 60 mm, 3 µm) with L1 packing and UV 250 nm wavelength, a flow rate of 1.0 mL/min, an injection volume of 10 µL, a column temperature of 40 °C ± 5 °C and a running time three times the retention time of rivaroxaban.

Dissolution conditions:

The medium consists of 0.4% (w/v) sodium dodecyl sulfate (SDS) in sodium acetate buffer, pH 4.5, with a volume of 900 ml, a paddle device, a speed of 75 rpm and a temperature of 37.0 °C ± 0.5 °C for 30 minutes.

Stability study:

This stability study was conducted under accelerated operation (40°C ± 2°C, 75% RH ± 5% RH for 1 and 3 months) and real time (30°C ± 2°C, 75% relative humidity (RH) ± 5 % RH for 3 months) Conditions as described in the following ASEAN Stability Study Climate Zone IV (b).

In vitro dissolution studies

In vitro dissolution studies for the dissolution of rivaroxaban in powder and solid dispersions (SDs) were performed using the USP Type II paddle device. The paddles were rotated at 75 rpm and maintained in 900 mL of pH 4.5 acetate buffer

(supplemented with 0.4% SDS) as dissolution medium at 37 ± 0.5 °C. Specific aliquots were removed at appropriate intervals (5, 10, 15, 20, 25, and 30 minutes) throughout the study to ensure subsidence conditions. The samples were filtered through a 0.45 mm Millipore filter in five milliliters. To maintain a constant volume, 5 mL of new dissolution liquid was added to the removed dissolution medium. The samples were then examined at a λmax of 248 nm using a UV/visible spectrophotometer (Patra et al., 2022).

Fourier Transform Infrared (FT-IR) Spectroscopy

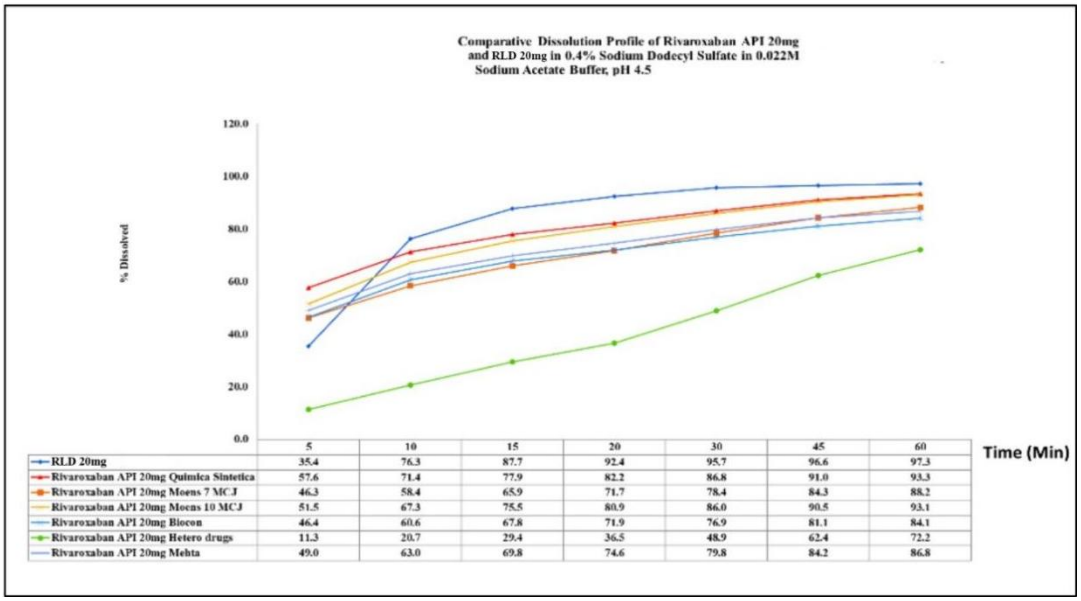
A Perkin Elmer Spectrum 100 FT-IR spectrophotometer was used to obtain the FT-IR spectra. Before analysis, the samples (solid dispersions or rivaroxaban) were carefully mixed in a ratio of 1:5 (sample:KBr) with potassium bromide, an infrared-transparent matrix, and then finely ground. The powders were carefully compressed using a hydraulic press for five minutes at a pressure of five tons to produce KBr discs. The wavelength range in which the spectra were recorded was between 4000 and 650 cm^{-1} (Patra et al., 2022).

X-ray Diffraction (XRD)

The lattice spacing was measured using a Guinier XDC-700 camera (Stockholm, Sweden) and X-ray diffraction. A PW Solution 1720 X-ray generator (Philips-Eindhoven, Netherlands), equipped with a crystal monochromator, generated CuKa radiation (151.540598 Å) (40 kV, 320 mA) that was applied to a small sample positioned in a rotating holder was. Room temperature was used for these experiments (Kang et al., 2022).

3. RESULTS

The solubility of the active ingredient, rivaroxaban was evaluated using samples from different suppliers, each with unique manufacturing processes and particle size ranges. The aim of this method was to identify the API particle size with optimal solubility properties. The intrinsic dissolution method was used to assess the solubility of the pure drug. Figure 1 shows that the API had an impressive solubility rate of 93.1%, exceeding that of samples from other manufacturers. This comprehensive analysis provides a clear conclusion on the solubility of the active ingredient rivaroxaban.



	5	10	15	20	30	45	60
RLD 20mg	35.4	76.3	87.7	92.4	95.7	96.6	97.3
Rivaroxaban API 20mg Quimica Sintetica	57.6	71.4	77.9	82.2	86.8	91.0	93.3
Rivaroxaban API 20mg Moens 7 MCJ	46.3	58.4	65.9	71.7	78.4	84.3	88.2
Rivaroxaban API 20mg Moens 10 MCJ	51.5	67.3	75.5	80.9	86.0	90.5	93.1
Rivaroxaban API 20mg Biocon	46.4	60.6	67.8	71.9	76.9	81.1	84.1
Rivaroxaban API 20mg Hetero drugs	11.3	20.7	29.4	36.5	48.9	62.4	72.2
Rivaroxaban API 20mg Mehta	49.0	63.0	69.8	74.6	79.8	84.2	86.8

Fig. 5: API intrinsic solubility dissolution with a marketed API

This study focused on analyzing the particle size of an active ingredient (Figure 2) using microscopy to distinguish drug particles from other components in tablets. During the analysis, around 800 particles were identified and divided into specific class intervals. A comparison was made with API, formulated tablets (F1-F5) and RLD. The main criterion for this study was the particle size with the desired selection of D90<10 µm for optimal resolution. The selected API had a D90 of 6.3 µm, while the RLD had a D90 of 5.3 µm. The analysis concluded that the selected API has a similar particle size to the RLD.

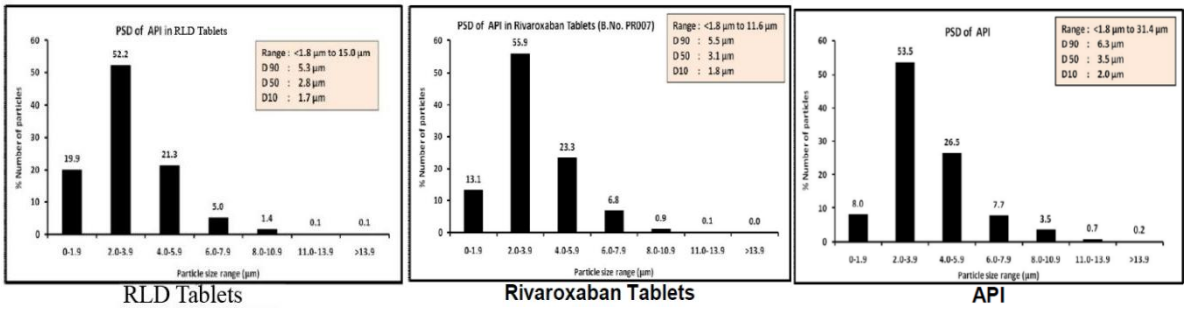


Fig. 2: Particle size analysis via hot-stage microscopy

Theta values (θ) in XRD analysis represent the angles at which X-rays are diffracted on a material's crystal lattice, indicating the interplanar distance. The 2θ value simplifies the interpretation of the diffraction pattern. All formulated tablets (F1–F5) showed similar peaks and patterns, confirming that the polymorphs used in F1–F5 were identical to those in the RLD, which was specifically identified as polymorph I and represents the thermodynamically stable form. Figure 3 shows that the X-ray diffraction analysis of all samples revealed consistent main peaks at 2θ values of 16.5°, 17.4°, 19.9°, 21.6°, 22.4°, 25.6°, and 26.6° revealed, indicating the presence of common components.

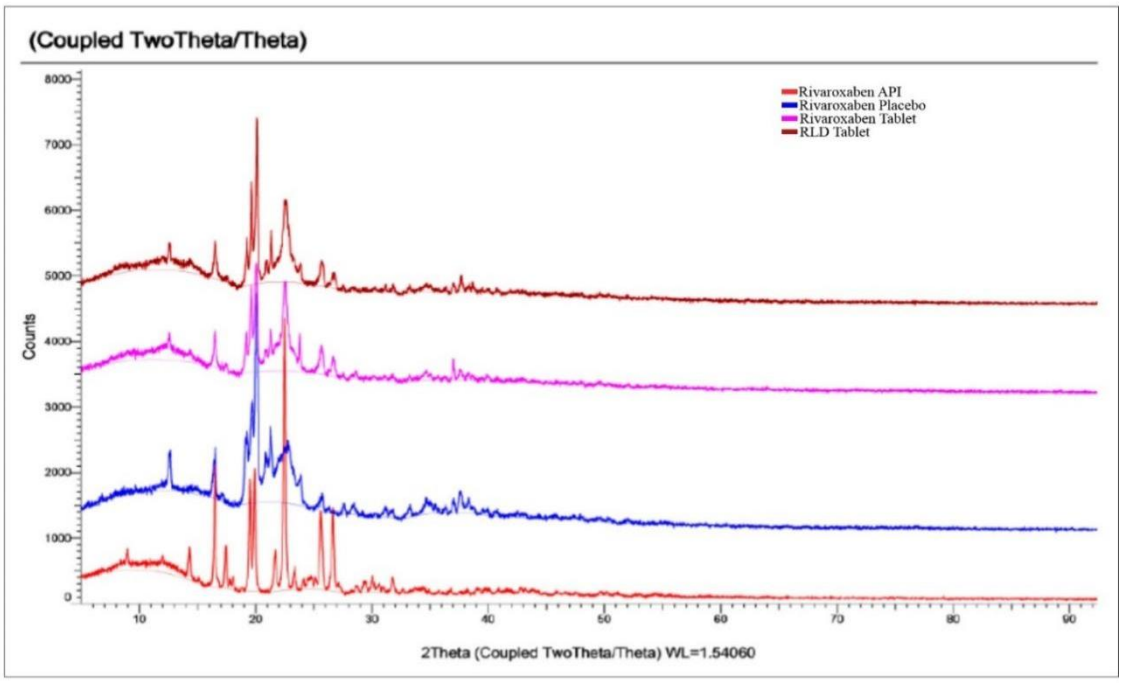


Fig. 3: Polymorphism via XRD

The SEM data (Figure 4 (a) and (b)) show that the granules in the RLD according to the fluid bed granulation technology have particle sizes in the range of 39.6 µm to 59.2 µm. This method produces smaller, uniform granules by swirling the particles and spraying on a liquid binder. The grains in the RLD have a narrow size distribution with smaller particles ranging from 39.6 µm to 48 µm, 55.3 µm and 59.2 µm. In contrast, the SEM data for the granules in F1-F5 showed particle sizes ranging from 48.6 µm to 107.2 µm, which were prepared via a different approach, i.e. solid dispersion using a conventional wet granulation technique.

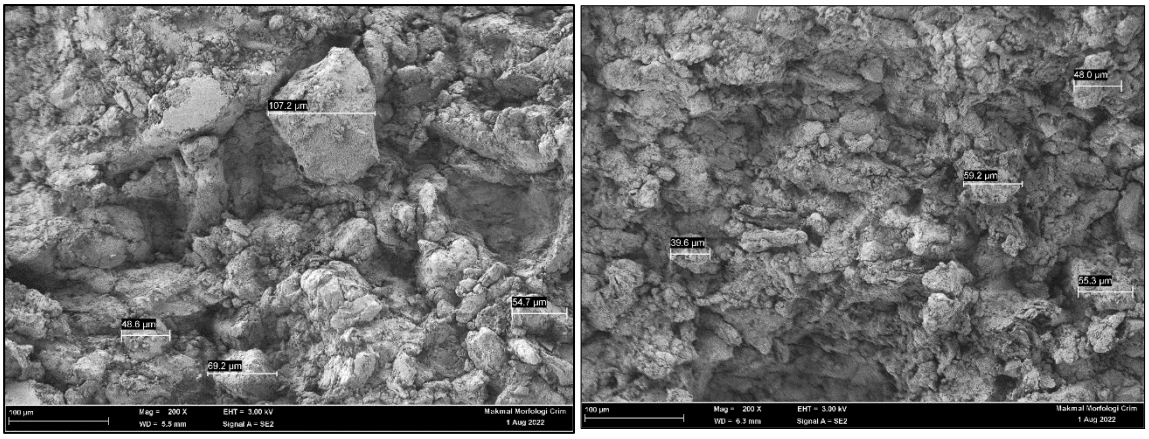


Fig. 4: SEM image: (a) RLD (b) F2

Table 2 shows a series of formulation trials aimed at improving the dissolution profile of rivaroxaban. All parameters were carefully maintained to ensure consistency as this research focused exclusively on solid dispersion carrier based formulations consisting of a precise blend of polymer and surfactant.

Table 2: Granulation parameters

Parameter	Time (min.)	Impeller speed (RPM)	Chopper speed (RPM/Amp)
Dry mixing	10	250	Off
Binder solution addition time	6	250	Off
Extra purified water time (Part 1)	1	250	Off
Extra purified water time (Part 2)	1	250	Off
Extra purified water time (Part 3)	1	250	Off
Kneading phase	1	250	Off

Formulation trials 1, 2 and 5 consistently demonstrate good flow properties based on Carr index and Hausner ratio, with low bulk and tap densities indicating well-packed particles and good flowability. Trials 3 and 4 have higher Carr Index and Hausner ratio values, indicating acceptable flow properties, but not as good as those in Trials 1, 2 and 5. Compared to those in Trials 3 and 4, the powder mixture The formulations in Experiments 1, 2 and 5 showed better flow properties, which slightly reduced the flow properties but were still passable.

Table 3: Flow properties of the lubricated blend

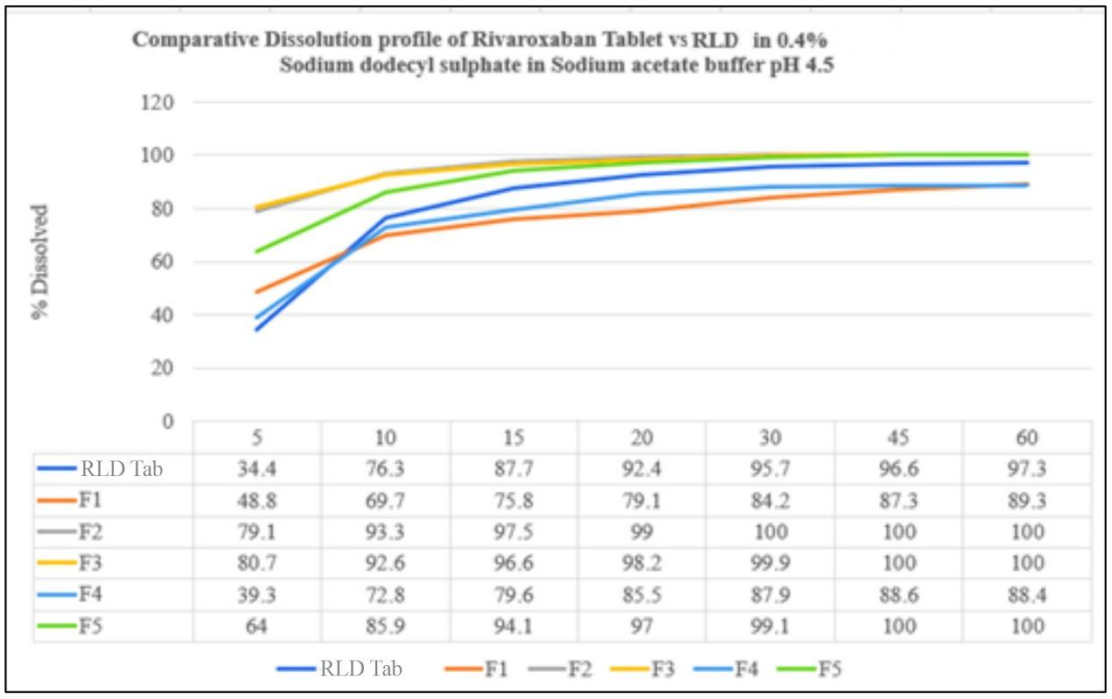
Formulation trial	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio	Flow properties
F1	0.61	0.70	12.85	1.15	Good
F2	0.50	0.58	13.79	1.16	Good
F3	0.50	0.67	25.37	1.34	Passable
F4	0.54	0.70	22.86	1.29	Passable
F5	0.62	0.73	15.06	1.18	Good

The tablet formulations (F1-F5) were developed to be as close as possible to the RLD in terms of weight, thickness, hardness and disintegration. Compared to those of RLD, the weights of F1-F5 ranged from 122.1 mg to 123.9 mg (88.9 mg).

Table 4: Post compression studies

Formulation Trial	Average weight (mg)			Thickness (mm)			Hardness (kP)			Disintegration time
	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	
F1	121.7	123.7	122.9	3.10	3.14	3.13	4.94	5.63	5.37	4 min. 3 s
F2	122.3	123.0	123.9	3.11	3.12	3.12	6.28	7.46	6.60	3 min. 50 s
F3	122.2	123.1	122.1	3.12	3.15	3.14	4.78	5.98	5.25	2 min. 44 s
F4	121.5	123.3	122.8	3.10	3.14	3.12	6.13	7.00	6.47	4 min. 14 s
F5	122.0	123.9	123.9	3.10	3.15	3.14	5.96	6.64	6.20	3 min. 29 s
RLD	88.1	89.6	88.9	2.91	2.93	2.92	5.75	6.09	5.93	4 min. 33 s

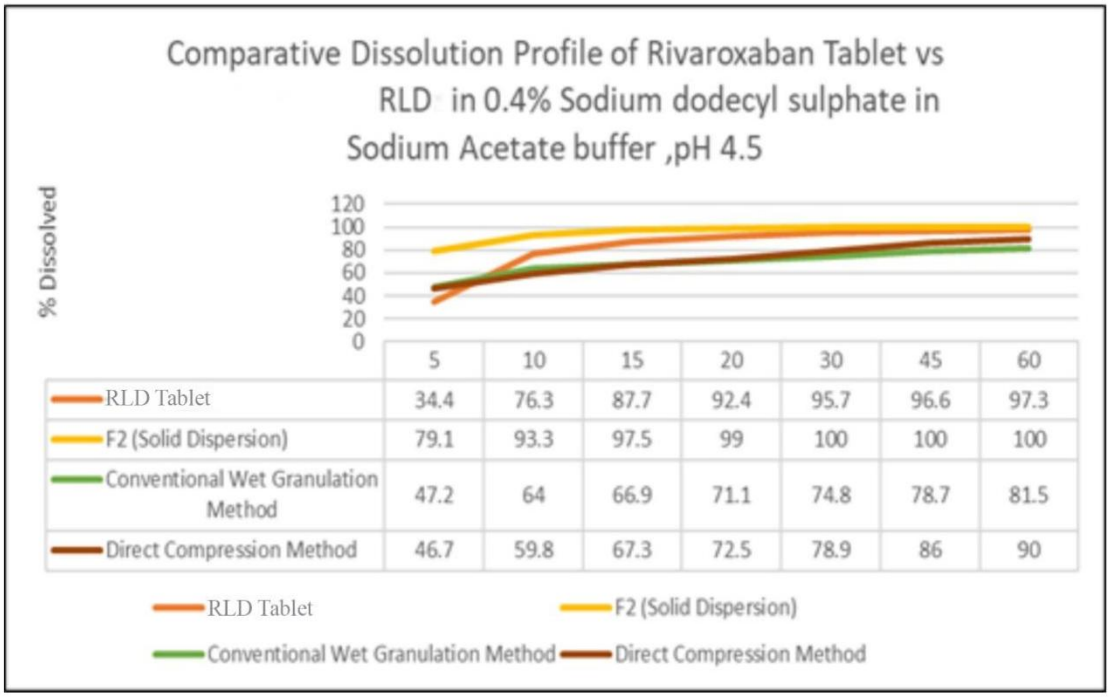
The dissolution data (Figure 5) shows the percentage of drug release over time for tablet formulations F1-F5. According to the USP dissolution of the rivaroxaban tablet, the Q value is 85% after 30 minutes, while the Q value of the RLD is 95.7%. Formulation F2 achieved a Q value of 100% after 30 minutes, indicating a rapid and efficient drug release profile. Formulations F3 and F5 also showed high Q values of 99.9% and 99.1%, respectively, at 30 minutes, indicating rapid and efficient drug release profiles. Formulations F1 and F4 had Q values of 84.2% and 87.9%, respectively, after 30 minutes, indicating slower drug release than the reference and other test formulations. Overall, the data provides valuable insights into the drug release process.



	5	10	15	20	30	45	60
RLD Tab	34.4	76.3	87.7	92.4	95.7	96.6	97.3
F1	48.8	69.7	75.8	79.1	84.2	87.3	89.3
F2	79.1	93.3	97.5	99	100	100	100
F3	80.7	92.6	96.6	98.2	99.9	100	100
F4	39.3	72.8	79.6	85.5	87.9	88.6	88.4
F5	64	85.9	94.1	97	99.1	100	100

Fig. 5: Dissolution profiles of F1-F5 vs RLD

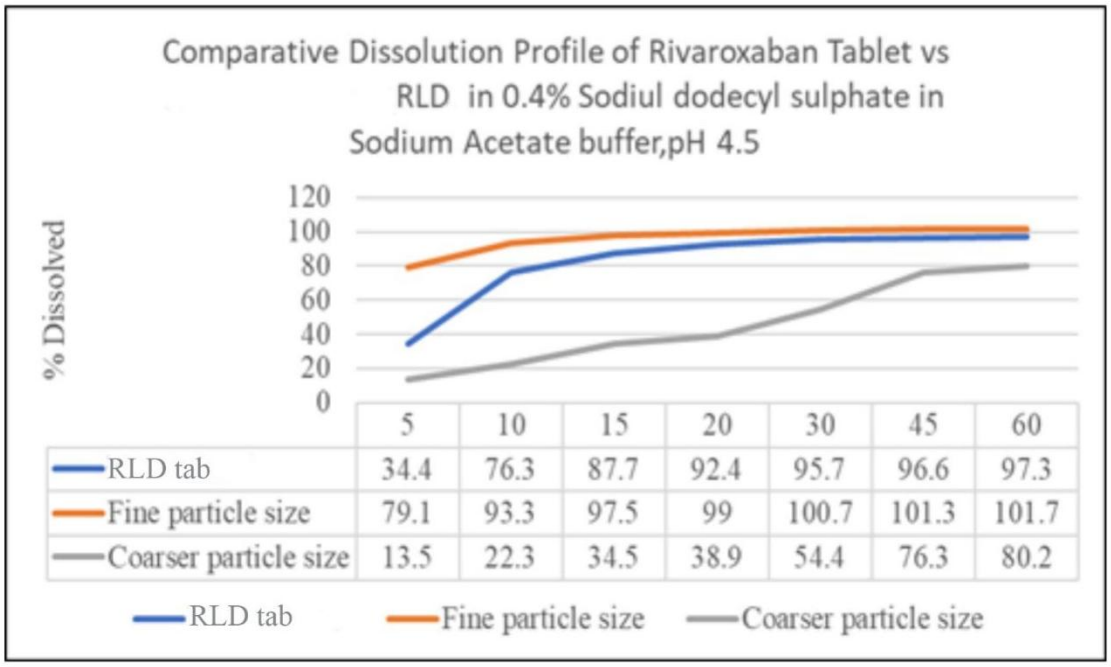
This study analyzed the drug release data for RLD, F2 (solid dispersion), a conventional wet granulation method and a direct compression method. Figure 6 shows that the drug release of the Innovator tablets gradually increased over time, with 95.7% of the drug released after 30 minutes. The F2 formulation, using a solid dispersion, showed rapid drug release that exceeded the Q value and reached 100% after 30 minutes.



	5	10	15	20	30	45	60
RLD Tablet	34.4	76.3	87.7	92.4	95.7	96.6	97.3
F2 (Solid Dispersion)	79.1	93.3	97.5	99	100	100	100
Conventional Wet Granulation Method	47.2	64	66.9	71.1	74.8	78.7	81.5
Direct Compression Method	46.7	59.8	67.3	72.5	78.9	86	90

Fig. 6: Impact of the manufacturing process with the optimized formula

The figure 7 shows the dissolution profiles of three different formulations, each with different particle sizes, at different times. The RLD shows an increase in the dissolution percentage with time, with 97.3% released after 60 minutes. Compared to the RLD, the formulation with a fine particle size has a faster dissolution rate, with higher percentages at each time point. The formulation with coarser particle size, such as B. API, has the slowest resolution rate, with a lower percentage after 30 minutes.



	5	10	15	20	30	45	60
RLD tab	34.4	76.3	87.7	92.4	95.7	96.6	97.3
Fine particle size	79.1	93.3	97.5	99	100.7	101.3	101.7
Coarser particle size	13.5	22.3	34.5	38.9	54.4	76.3	80.2

Fig. 7: Impact of Particle Size

A real-time stability study of a specific drug product was conducted to evaluate the product's appearance, average tablet weight, and hardness values. The target weight was 123.6 mg, with an acceptable variability of ± 7.5%. The average tablet weight remained within the specified range, with values of 122.7 mg and 122.8 mg, indicating stability. The hardness range was 3-12 (kp), with consistent values of 7 kp, indicating structural integrity and hardness. The tablets disintegrated within

the required time frame, with dissolution times of 4 min. 9 s and 3 min. 24 s, indicating good disintegration characteristics. The minimum dissolution rate was 96%, and the maximum and mean dissolution rates were 99% and 98%, respectively, indicating consistent drug release during the stability study.

The accelerated study revealed tablets with disintegration times of 2 min, 38 s and 4 min, 23 s, and dissolution values of 96%, 100%, and 98%, respectively. These results indicateds that the tablets maintain good dissolution properties and meet the dissolution requirements under accelerated conditions. The results showed that the tablets perform as intended even under accelerated conditions.

Table 5: Stability studies at real time (30°C ± 2°C/60% RH ± 5%)

Test	**Shelf - life specification**	**Test frequency (months)**	
		Initial	**T3**
Appearance	Round, dark red, biconvex film coated tablet debossed with '20' on one side and plain on other side	Complies	Complies
Average Tablet Weight	123.6 mg ± 7.5%	122.7 mg	122.8 mg
Hardness	3 to 12 kp	7 kp	7 kp
Disintegration Time	Not more than 30 min.	04 min. 09 s	03 min. 24 s
Dissolution	Not less than 80% (Q) of the labelled amount of Rivaroxaban is dissolved in 30 min.	Min : 97% Max : 100% **Mean : 99%**	Min : 96% Max : 100% **Mean : 98%**

Table 6: Stability studies at acceleration times (40°C ± 2°C/60% RH ± 5%)

Test	**Shelf - life specification**	**Test frequency (months)**	
		Initial	**T3**
Appearance	Round, dark red, biconvex film coated tablet debossed with '20' on one side and plain on other side	Complies	Complies
Average Tablet Weight	123.6 mg ± 7.5%	123.4 mg	123.4 mg
Hardness	3 to 12 kp	7 kP	7 kP
Disintegration Time	Not more than 30 min.	02 min. 38 s	04 min. 23 s
Dissolution	Not less than 80% (Q) of the labelled amount of Rivaroxaban is dissolved in 30 min.	Min : 95% Max : 98% **Mean : 97%**	Min : 96% Max : 100% **Mean : 98%**

The data shown in Figure 8(a-e) indicated that FT-IR spectrum that used to analyse the RLD, and F2 (optimized formulation) over three months for a stability study. The analysis confirmed no detectable interaction between the excipient and the drug in the formulation, demonstrating the compatibility of the selected excipients with the drug molecule. This ensures that the drug remains chemically stable and maintains its integrity within the formulation. FT-IR analysis also revealed that the polymorphic form of the drug remains in the amorphous state in the formulated product, validating the stability and performance of the product.

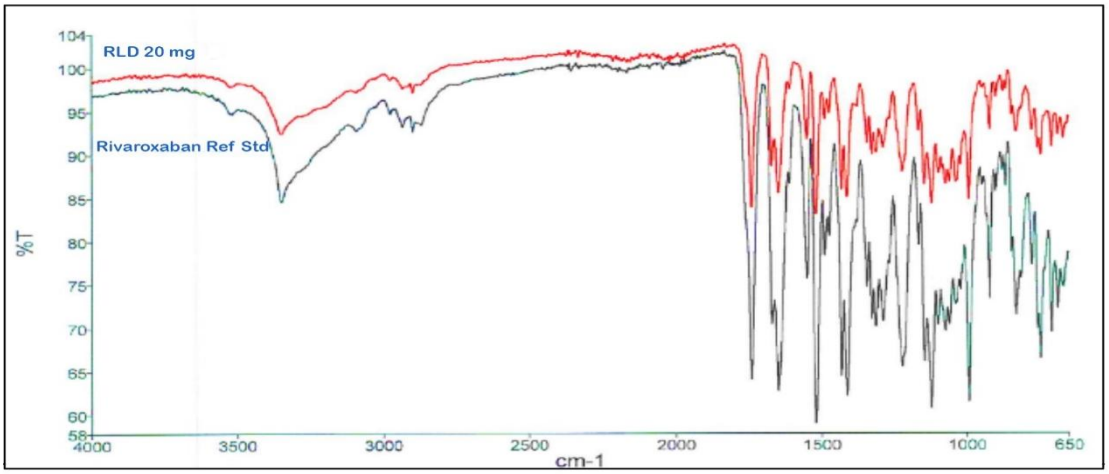


Fig. 8: (a) – IR spectrum of Reference standard vs RLD

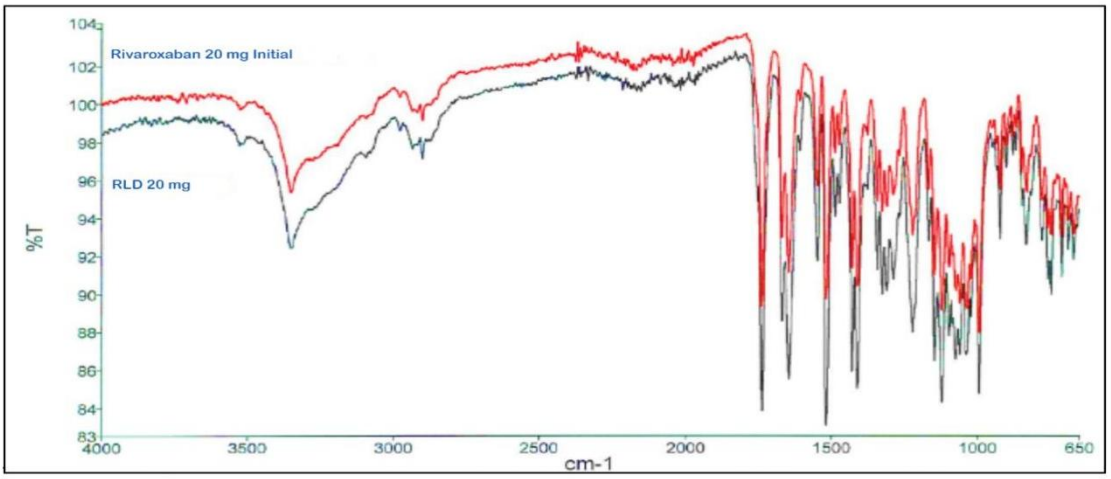


Fig. 8: (b) - IR spectrum of T0 test sample vs RLD

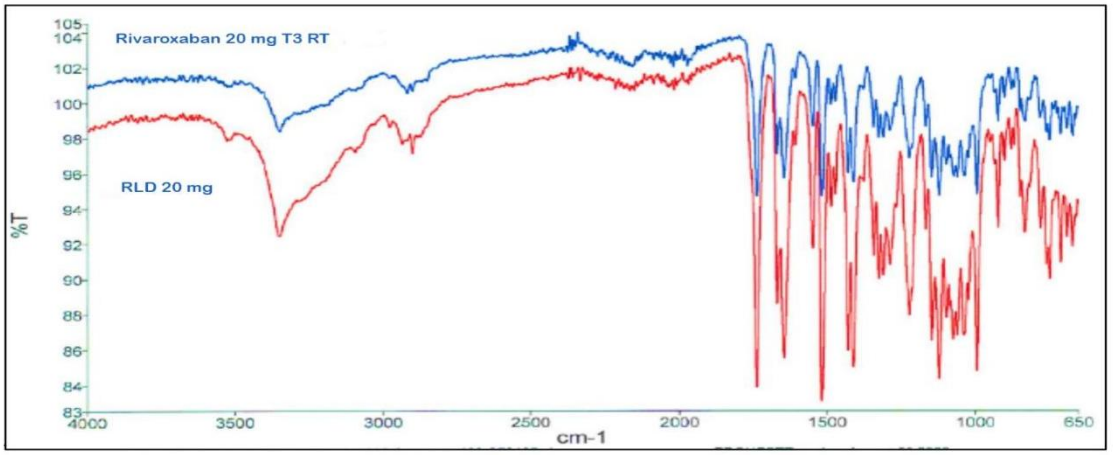


Fig. 8: (c) - IR spectrum of T3 Real-Time Sample vs RLD

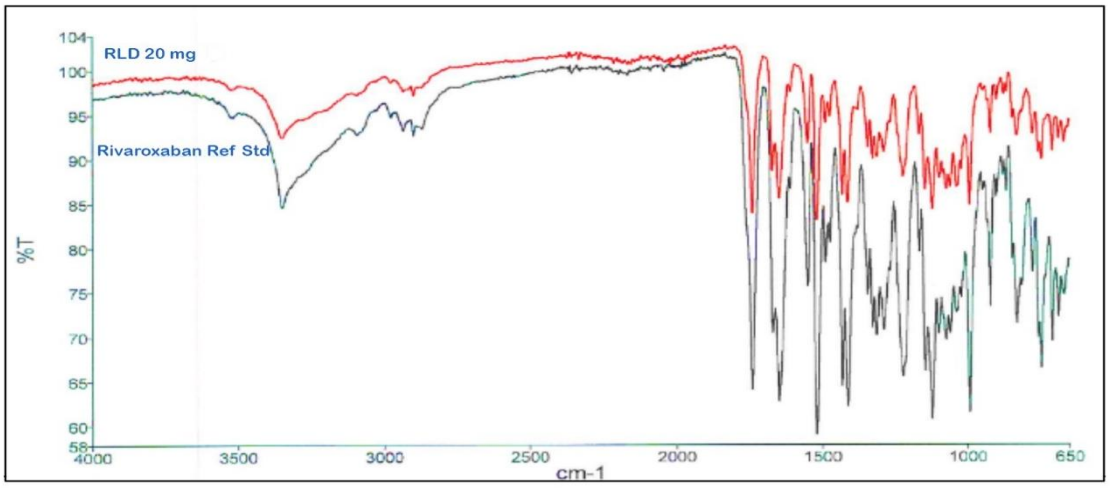


Fig. 8: (d) - IR spectrum of T1 Accelerated Sample vs RLD

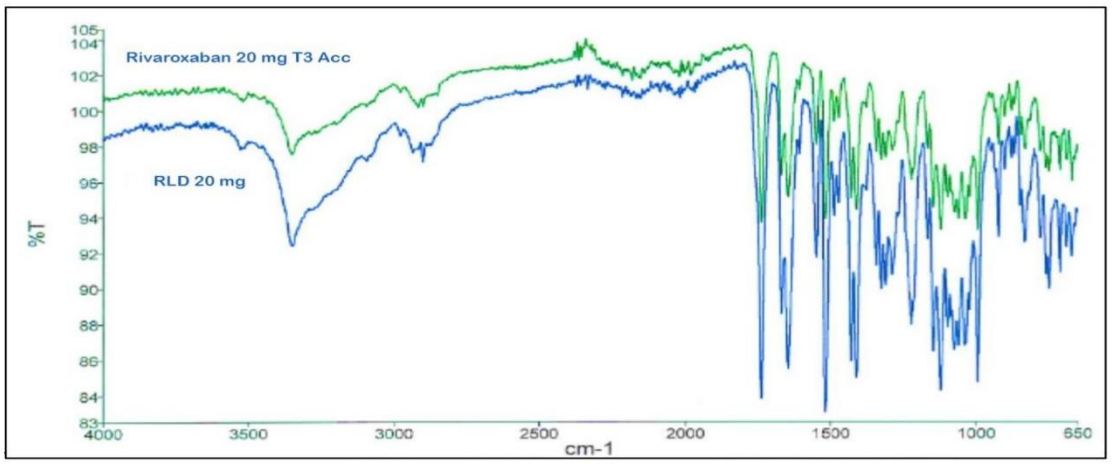


Fig. 8: (e) - IR spectrum of T3 Accelerated sample vs RLD

4. DISCUSSION

This study enlightens the solubility and dissolution behavior of rivaroxaban API and its formulated products were investigated comprehensively using a combination of analytical and manufacturing techniques. Key findings from solubility assessments, particle size analysis, and formulation trials provided critical insights into optimizing the performance of rivaroxaban tablets. The intrinsic dissolution analysis revealed that the selected API sample exhibited a high solubility rate of 93.1% (Figure 1), significantly surpassing other samples. This outcome underscores the importance of sourcing API with superior solubility characteristics. Particle size analysis further highlighted the importance of maintaining a D90 value below 10 µm for optimal dissolution. The selected API had a D90 of 6.3 µm, closely matching the reference listed drug (RLD) at 5.3 µm (Figure 2), ensuring similar dissolution performance. These findings reaffirm the pivotal role of particle size in drug solubility and bioavailability. XRD analysis (Figure 3) confirmed that all formulations shared identical polymorphic characteristics, specifically polymorph I, the thermodynamically stable form. This consistency ensures robustness and stability across formulations. Additionally, SEM analysis revealed differences in granule size distributions between RLD and test formulations due to varying granulation techniques (Figure 4 (a) and (b)). This technique allows the API to be incorporated into a polymer matrix but may result in a broader particle size distribution. The difference in granule sizes can be attributed to the different granulation technologies used in their formulation.

Flow property evaluations (Table 3) showed that formulations F1, F2, and F5 exhibited superior flowability based on Carr's index and Hausner's ratio. In contrast, formulations F3 and F4 demonstrated marginally passable flow properties, indicating potential challenges in manufacturing consistency for these formulations. The ability to achieve good flow properties directly influenced tablet uniformity and quality. Table 4 shows that the tablet formulations (F1-F5) were developed to closely match the RLD in terms of weight, thickness, hardness, and disintegration. To ensure bioequivalence for the lowest strength, the weight was adjusted to be dose-proportional, allowing a biowaiver for lower strength. This strategic decision aims to reduce

bioequivalence study costs while maintaining high-quality and efficacy standards. The test sample demonstrates the same level of safety and efficacy as the RLD, providing a reliable alternative at a more affordable cost. The thickness and hardness were kept within constant limits, as the primary focus was on improving the solubility. In line with the quality by design (QBD) approach, only one parameter was altered at a time to enhance the product's robustness.

According to the USP dissolution of the rivaroxaban tablet, the specification to achieve the dissolution rate is 85% at 30 minutes; this means that more than 85% of the active ingredient must be dissolved after 30 minutes. Figure 5 showed the dissolution profiles and highlighted the superior performance of formulation F2, which achieved a Q value of 100% at 30 minutes, surpassing the USP specification of 85%. Other formulations (F3 and F5) also demonstrated efficient drug release, with Q values above 99%. However, formulations F1 and F4 displayed decline in dissolution rates due to formulation-specific factors, such as the increased HPMC concentration in the formulations, which reduced the release rate. The rate further decreased with increasing HPMC concentration. Optimizing excipient ratios and granulation parameters proved essential in achieving the desired dissolution profiles. The SLS concentration was optimized within 0.5% to 1.00% and reached saturation at this stage, confirming the ideal concentration for the desired results (Choi et al., 2022). Compared to the faster and more effective release profiles observed with F2 and RLD (Figure 6), the conventional wet granulation method and the direct compression method resulted in slower drug release profiles, namely 74.8% and 78.9%, respectively (Patra et al., 2022). Moreover, the figure 7 highlights the importance of particle size in drug dissolution, where a fine particle size promotes faster and more complete drug release, while a coarser particle size can result in delayed and incomplete dissolution The finer particle size formulation has a higher dissolution rate, likely due to the larger surface area of smaller particles, resulting in faster drug release and improved bioavailability. The formulation with coarser particles has a slower dissolution rate, resulting in a delayed and less extensive drug release. (Bhalani et al., 2022).

Additionally, the stability studies under real-time (Table 5) and accelerated conditions (Table 6) confirmed the structural and chemical integrity of the tablets over time. The consistent dissolution rates (≥96%) and disintegration times within acceptable ranges indicate reliable performance across varying storage conditions. FT-IR spectrums (Figure 8(a-e)) further validated the absence of drug-excipient interactions and the maintenance of the drug's amorphous state, ensuring stability and efficacy throughout the shelf life. This study successfully optimized rivaroxaban tablet formulations by integrating solubility enhancement strategies, precise particle size control, and robust manufacturing techniques. The data demonstrate that formulation F2, utilizing solid dispersion technology, exhibits dissolution behavior comparable to or better than the RLD, ensuring therapeutic equivalence. The application of advanced analytical tools and a systematic formulation approach underscores the importance of tailoring manufacturing processes to achieve high-quality pharmaceutical products. Besides, the study highlights the significance of optimizing particle size and manufacturing techniques to enhance the solubility, dissolution rate, and bioavailability of rivaroxaban. Advanced analytical tools like XRD, SEM, and FT-IR spectroscopy ensured polymorphic consistency, structural stability, and excipient compatibility, contributing to reliable formulation development.

However, the study has limitations. It focuses narrowly on D90 particle size without exploring additional metrics like D50, and lacks in vivo pharmacokinetic data to confirm bioavailability improvements. The excipient selection was limited, and only specific formulation techniques were evaluated, potentially restricting broader applicability. Additionally, the short-term stability studies and the absence of commercial-scale evaluations leave questions about long-term robustness and scalability. Addressing these limitations could enhance the findings' relevance and ensure broader, more robust applications in drug development. The present study drives the future research to focus on conducting in vivo pharmacokinetic studies to validate the in vitro dissolution data and ensure therapeutic efficacy. Investigating alternative manufacturing techniques along with a broader excipient selection and Long-term stability studies are needed to confirm the formulations' robustness over time.

5. CONCLUSION

This study emphasizes the importance of reducing the particle size and increasing the surface area in enhancing the drug solubility, dissolution rate, and bioavailability. It also discusses the use of solid dispersions containing linear polymers to create larger, more porous particles for faster drug release. The combination of HPMC and SLS in a formulation can overcome the challenges of poorly soluble drugs by forming a hydrogel layer around drug particles and breaking down dissolution barriers. The amorphous state of the drug also plays a crucial role in enhancing drug release by eliminating the energy barrier associated with breaking up the crystal lattice during dissolution. This strategy holds great promise in advancing pharmaceutical technology, enabling the development of more effective drug formulations that can overcome the limitations of poorly soluble drugs, resulting in superior therapeutic outcomes for patients. These findings have significant implications for the formulation of pharmaceutical products with increased solubility, dissolution rates, and bioavailability. The cost-effectiveness of the solid dispersion technique makes it a viable alternative to fluid bed granulation. Further research could lead to more advanced and tailored drug formulations that cater to specific drug properties and patient needs, enhancing drug performance and patient well-being.

List of abbreviations

API: Active Pharmaceutical Ingredient

BCS: Biopharmaceutics Classification System

CMS: Critical Micelle Concentration

FT-IR: Fourier Transform Infrared

HPMC: Hydroxy propyl methyl cellulose

PSD: Particle size distribution

RH: Relative humidity

RLD: Reference Listed Drug

RMG: Rapid mixer granulator

SDS: Sodium dodecyl sulfate

SEM: Scanning Electron Microscopy

SLS: Sodium lauryl sulfate

USP: United States Pharmacopeia

XRD: X-Ray Diffraction

Declarations

Ethics approval and consent to participate

Not Applicable

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