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RIVAROXABAN-EXCIPIENT COMPATIBILITY STUDIES FOR ADVANCED DRUG DELIVERY SYSTEMS DEVELOPMENT

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ABSTRACT

The main objective of the present study was to the preformulation studies were performed to know the physico-chemical and mechanical properties of Rivaroxaban for formulation development of ODTs. The drug-excipient compatibility studies were conducted to characterize the drug Rivaroxaban present in Orodispersible tablets (ODTs). The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Preformulation, formulation and evaluation of Rivaroxaban to avoid problems associated with conventional delivery system such as limited permeation, low dissolution and bioavailability and also to improve bioavailability and oral anticoagulant effect. In the present study that the compatibility was assessed by, FTIR spectroscopy, and melting point apparatus, precompression parameters and powder flow properties. Results showed that physical mixtures of Rivaroxaban and various excipients as mannitol, microcrystalline cellulose as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants sodium lauryl sulfate as wetting agents were evaluated for preformulation studies parameters. It was concluded that the drug Rivaroxaban was found to be compatible with various excipients which were selected for the formulation development of the Rivaroxaban ODTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

KEYWORDS: Rivaroxaban, Anticoagulant, Compatibility, Excipients, Development, , Preformulation, Drug delivery systems.

INTRODUCTION

Preformulation Studies[1-150]

The safety, efficacy, quality and stability of a formulation are major concepts of any API development process. In API development process, a detailed characterization of the API and other formulation components is usually carried out during the preformulation stage. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

One of the objectives of this study is to development of drug delivery systems by building scientific pharmaceutical research information depend on formulation scientists to join the knowledge and experience as well as experimental and practical results of this study with regard to information in previous studies, and approved references. It was found to be that the most important concepts and basics of preformulation studies such as definitions, methods, conclusion, idea, and types of pharmaceutical analysis techniques using in evaluation of preformulation studies parameters, in this study that we focused on developing drug delivery systems and linking the formulation development to establish the basics of pharmaceutical research in

studying the drug-excipient compatibility, dug with various excipients, which is important for the safety, effectiveness, quality, formulation, stability, bioavailability, and pharmacokinetics of the drug etc.

Preformulation research were evolved in 1950. It is defined as the phase of research and development in which preformulation studies characterize physical and chemical properties of a drug molecule in order to develop safe, effective, bioavailability and stable dosage form. In preformulation studies, physicochemical properties of drug molecules are characterized either alone or in combination with excipients. Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API).

Preformulation Study Includes: Determination of physical chemical properties of API substance with the goal of developing a new drug which is safe stable and efficacious, each API, has intrinsic chemical and physical properties that were considered prior to the development of pharmaceutical formulation, the purpose of preformulation study is to generate useful information for the formulator in the development of stable and bioavailable dosage form, inappropriate preformulation study results in poor stability of active ingredients increase the overall cost of development and increased development time, preformulation studies help to fortify the pharmaceutical scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improve product quality, promote the implementation of new technologies, aids policy development and regulatory decision making and after compiling all data it is transferred to the development pharmacist and for the day work on formulation of dosage form.

Preformulation Study Objectives: To establish the Physico-chemical parameters of a new API entity, determine its kinetics and stability, establish its compatibility with common excipients, it provides insights into how drug products should be processed and stored to ensure their quality, estimate problem may arise during formulation that is stability problem poor *in-vivo* dissolution, poor bioavailability, to interpret BCS classification of drugs and its significance and develop optimal drug delivery system.

Drug-Excipient Compatibility Study: The primary objective of this investigation was to identify a stable storage condition for API in solid state and identification of compatible excipients for its formulation. Incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance.

Dosage Forms: DF contain API and pharmaceutical excipients, which are intended to generate an ideal formulation and manufacturability of pharmaceutical products, thereby enabling a much safer and more effective administration. Pharmaceutical excipients are ideally inactive and have no impact on the stability or therapeutic effect of the active ingredient. On the other hand, there are studies that have presented that some pharmaceutical excipients are just allegedly described as inactive ingredient. Some pharmaceutical excipients have the capacity to affect API, efficacy by affecting its pharmacokinetics. Excipients can affect the physical and chemical form of pharmaceuticals by several factors such as hydrogen bond interaction, polymorphic conversion, and others. Accordingly, drug-excipient compatibility should be conducted so as to determine any drug-excipient interactions that may obstruct the stability, bioavailability, and manufacturability of pharmaceutical dosage forms.

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability are not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

In the present study, it was proposed to drug-excipient compatibility studies of Rivaroxaban, with commonly different excipients using for formulation development of Orodispersible tablets ODTs.

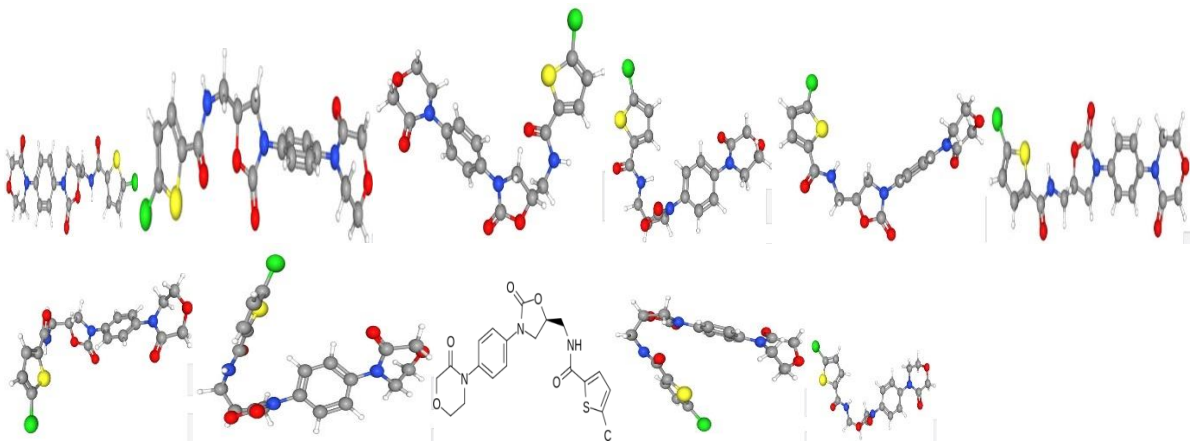
MATERIALS AND METHODS

Rivaroxaban and Acetonitrile were gift from (Modern Pharmaceutical Industry Company-Yemen). Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium, Avicel 102, Mannitol, PVP K30, Sodium Lauryl Sulfate, Aerosil, Magnesium Stearate, Talc, Aspartame, Saccharin Sodium, Vanilla Flavor, Distilled Water, Sodium Hydroxide, Monobasic Potassium Phosphate and Potassium Bromide were gift from (Shaphaco Pharmaceutical Industry Company-Yemen).

Evaluation of Drug–Excipient Compatibility Studies Methods[55-356]

Table 1: Rivaroxaban Data.

Characterization of Rivaroxaban



Rivaroxaban Structure and 3D Conformer

Chemical Structure	(S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl] oxazolidin-5-yl] methyl} thiophene-2-carboxamide	**Appearance**	Non-hygroscopic, white to yellowish powder.
Chemical Formula	C19H18ClN3O5S	**Solubility**	slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in

			water and aqueous media.
Molecular Weight	435.88 g·mol−1	**BCS**	Class-II Drug
Action and Use	Inhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways. FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, factor II and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and cata-lyzes the conversion of fibrinogen to fibrin. Rivaroxaban is an anticoagulant which binds directly to factor Xa. Thereafter, it effectively blocks the amplification of the coagulation cascade, preventing the formation of thrombus. Prophylaxis of venous thromboembolism following knee replacement surgery Prophylaxis of venous thromboembolism following hip replacement surgery Treatment of deep-vein thrombosis. Treatment of pulmonary embolism Prophylaxis of recurrent deep-vein thrombosis. Prophylaxis of recurrent pulmonary embolism Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischemic attack, age 75 years, or diabetes mellitus. Prophylaxis of atherothrombotic events following an acute coronary syndrome with elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel) Prophylaxis of atherothrombotic events in patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischemic events (in combination with aspirin).	**Duration of Treatment**	Chronic
Pharmacokinetics of Rivaroxaban			
Drug	Rivaroxaban is rapidly absorbed	**Drug Distribution**	Plasma protein binding is about

Absorption	and reaches peak plasma concentration in 2-4 hours. Bioavailability of the 10 mg dose is >80%. However, the 15-20 mg dose have a lower bioavailability if taken in the fasted state and consequently should be taken with food.		92% to 95% The steady state Vd is 50 L.
Drug Metabolism	Approximately two-thirds of the dose is metabolized. It is metabolized by CYP3A4, CYP3A5, CYP2J2 and CYP-independent mechanisms.	**Drug Excretion**	Urine (66% primarily via active tubular secretion [36% as unchanged drug; 30% as inactive metabolites]); feces (28% [7% as unchanged drug; 21 % as inactive metabolites])Systemic clearance is approximately 10 L/h, so Rivaroxaban is considered a drug with low clearance. Renal clearance is ~3-4 L/h.
The Elimination Half-Life (T1/2)	The terminal half-life is 5-9 hours in adults and 11-13 hours in the elderly. Time to peak plasma :2-4 hours.	**Availability**	Tablets: 2.5mg, 10mg, 15mg, 20mg.

Table 2: Pharmaceutical Excipients Data.

Nonproprietary Name	Chemical Name	Functional Category	Concentration%	Solubility	Incompatibilities	Notes
Croscarmellose Sodium (Ac-Di-Sol)	Cellulose, carboxymethyl ether, sodium salt, crosslinked**.**	Tablet and capsule disintegrant.	0.5-5% 10-25%	Insoluble in water	Incompatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.	White or grayish-white powder
Crospovidone (PVPP)	1-Ethenyl-2-pyrrolidinone homopolymer	Tablet disintegrant.	2–5%	Practically insoluble in water	Compatible with most organic and inorganic pharmaceutical ingredients.	Hygroscopic powder
Sodium Starch Glycolate (Explotab)	Sodium carboxymethyl starch	Tablet and capsule disintegrant.	2–8%	Gives a translucent suspension in water.	Incompatible with ascorbic acid.	Very hygroscopic
Microcrystalline Cellulose (Avicel PH102)	Cellulose	Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant.	5–20% 20–90%	Practically insoluble in water	Incompatible with strong oxidizing agents.	Crystalline powder
Mannitol (Emprove)	Mannitol	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent, tonicity agent.	10–90%	Freely soluble in water	Incompatible with may be salted out by potassium chloride or sodium chloride. Sodium cephapirin. xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron.	Crystalline powder
Magnesium Stearate (magnesium salt)	Octadecanoic acid magnesium salt	Tablet and capsule lubricant.	0.25 - 5.0%	Practically insoluble in water	Incompatible with strong acids, alkalis, and iron salts.	Greasy
PVP K30	E1201, Kollidon, Plasdone, polyvidone, polyvinylpyrrolidone, PVP;1vinyl-2- pyrrolidinone polymer.	Disintegrant, tablet binder.	2.0–5.0%	Greater than 10% solubility in water, methanol,	compatible in solution with a wide range of inorganic salts, natural and synthetic	White to yellowish-white amorphous powder.

				PG….	resins, and other chemicals.	
Talc	Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac Pharma, magnesium hydrogen metasilicate. Mg6(Si2O5)4(OH)4.	Anticaking agent, glidant, diluent, lubricant.	1.0–10.0% 5.0–30.0%	Practically insoluble in dilute acids and alkalis, organic solvents, and water.	Incompatible with quaternary ammonium compounds.	is a very fine, white to grayish-white, crystalline powder.
Aspartame	3-Amino-N-(a carboxyphenethyl) succinamic acid N-methyl ester; 3-Amino-N- (a methoxycarbonylphenethyl) succinamic acid;	Sweetening agent. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.	In practice, the small quantity of aspartame consumed provides a minimal nutritive effect.	Slightly soluble in ethanol (95%); sparingly soluble in water. At 208C the solubility is 1% w/v at the isoelectric point (pH 5.2).	incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols.	occurs as an off white, almost odorless crystalline powder with an intensely sweet taste
Saccharin Sodium	1,2-Benzisothiazolin-3-one 1,1-dioxide, sodium salt, Crystallose, E954, gendorf 450, sucaryl sodium	Sweetening agent. Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 300–600 times that of sucrose.	0.02–0.5% w/w.	Readily dissolved by dilute ammonia solutions, alkali hydroxide solutions, or alkali carbonate solutions. 1 in 290 water.	Saccharin can react with large molecules. Saccharin sodium does not undergo Maillard browning.	white crystals or a white crystalline powder.
Aerosil	Aerosil; Cab-O-Sil, Cab-OSil M-5P, colloidal silica, fumed silica, fumed silicon dioxide, SAS, silica colloidalis anhydrica	Adsorbent; anticaking agent glidant; viscosity-increasing agent	0.1–1.0% 2.0–10.0% widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient.	Practically insoluble in organic solvents, water. -hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system.	Incompatible with diethylstilbestrol preparations.	A submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.
Sodium Lauryl Sulfate	Dodecyl alcohol hydrogen sulfate, sodium salt, dodecyl sodium sulfate, dodecyl sulfate sodium salt, Elfan 240. C12H25NaO4S	Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and	10% 0.5–2.5% 1.0–2.0%	Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and	incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc	white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter

		capsule lubricant; wetting agent.		ether.		taste, and a faint odor of fatty substances
Vanilla Flavor Ethyl Vanillin	Bourbonal; ethylprotal; ethylprotocatechuic aldehyde; 4-hydroxy3-ethoxybenzaldehyde; Rhodiarome; vanillal. C9H10O3	Flavoring agent. also used in perfumery.	0.01% Ethyl vanillin is generally regarded as an essentially nontoxic and nonirritant material.	Freely soluble in Alkaline hydroxide solutions. Soluble in Glycerin, Propylene glycol In Water 1 in 250.	Ethyl vanillin is unstable in contact with iron or steel, forming a red colored, flavorless compound. In aqueous media with neomycin sulfate or succinyl sulfathiazole, tablets of ethyl vanillin produced a yellow color.	White or slightly yellowish crystals with a characteristic intense vanilla odor and flavor.

According to Rivaroxaban and excipients data as shown in Tables 1 and 2, it was selected that the different excipients to preformulation study with Rivaroxaban in the present study, the equipments used as shown in Table 3.

Table 3: The Equipment's Used.

No	Equipment's
1	Fourier Transform Infrared Spectrophotometer
2	UV/VIS Spectrophotometer
3	Melting Point Tester
4	Moisture Tester
5	Density Tester
6	pH Meter
7	Electronic Balance
8	Rotary Tablet Compression Machine
9	Accelerate Stability Study Chamber

Drug Identification Test

Determination of The Organoleptic Properties

The organoleptic properties like color, odor and taste of the API were evaluated. Color a small quantity of Rivaroxaban was taken in a butter paper and viewed in well illuminated place. Taste and odor very less quantity of Rivaroxaban was used to assess the taste with the help of tongue as well as smelled to get odor. The organoleptic properties of the API substance were assessed.

UV Scanning of Rivaroxaban in Phosphate Buffer at PH 6.8

The concentration of Rivaroxaban10µg/ml solution was prepared in phosphate buffer pH 6.8 and was subjected to scanning under UV visible spectrophotometer, between the range 200-400nm.The λmax was found to be at 248 nm.

Preparation of Standard Calibration Curve

Preparation of Phosphate Buffer (pH=6.8): 0.896 g of NaOH and 6.804 g of KH2PO4 dissolved in sufficient quantity of water, the volume was completed to 1000 ml with distilled water and mixed well by sonication. An accurately weighed 1 mg of Rivaroxaban was dissolved in 100ml of phosphate buffer (pH,6.8) to get a concentration of 10 µg/ml. Aliquots of stock solution were pipetted out ranging from volume 1 ml, 2 ml, 3 ml, 4 ml and 5 ml in a 5 ml volumetric flask and the volume was adjusted to 5 ml with phosphate buffer (pH6.8) to produce concentration of 2, 4, 6, 8, and 10 µg/ml respectively. Absorbance of the above solutions was measured at 248 nm by UV visible spectrophotometer against a blank of phosphate buffer solution. The standard calibration curve was obtained by plotting absorbance verses concentration in µg/ml.

Preformulation Studies

Preformulation studies are initiated to define the physical and chemical properties of the agent. The key goals of preformulation studies are to ensure the delivery of drug product with acceptable stability, bioavailability, and manufacturability.

Melting Point Determination of Rivaroxaban

Melting Point: Melting point of the Rivaroxaban was determined by capillary method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid.

Drug-Excipient Compatibility Studies

A physical mixture including Rivaroxaban and excipient was created in a 1:1 ratio, and it was subjected to analytical techniques such as FTIR spectroscopy. FTIR, of both pure drug and physical mixes were obtained, and the spectra of the both drug and mixture of excipient with drug were compared to look for any incompatibilities.

FTIR Spectroscopy Study

FTIR study KBr-disc method was used to record the FTIR spectra and KBr pellets were made in 1:100 ratio of sample and KBr. FTIR spectra was recorded using FTIR spectrum in a range of 4000-400cm^{-1}. Different functional groups of test compound for distinctive vibrational frequencies are identified using FTIR spectroscopy. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wavenumbers and appearance or disappearance of characteristic peaks of functional groups for pure API in physical mixture. FTIR spectroscopic study was

performed to check the compatibility between API, and different excipients in amount (5mg:5mg) as ratio (1:1) as shown in Table 5. The FTIR spectra of a API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

Preparation of IR Samples

The sample was determined by the disc method. Triturate 5mg of the substance to be examined with 300-400 mg of finely powdered and dried potassium bromide R or potassium chloride R. Each excipient was mix with Rivaroxaban equally then of potassium bromide is added to the mixture. Carefully grind the mixture, spread it uniformly in a suitable die, and submit it to a pressure of about 800 MPa (8 $t \cdot cm^{-2}$). Then the tablets were inserted to the device and the Infrared spectra was recorded at mild-infrared light in wavenumber range of 4000 cm^{-1} to 400 cm^{-1}. After that the spectra were compared with the reference.

Infrared Spectral Study of Samples in Room Condition

Compatibility studies were performed by preparing blend of different excipients with Rivaroxaban in room condition as shown in Table 5.

Infrared Spectral Study of Samples after Stored One Month

Compatibility studies were performed by preparing blend of different excipients with drug and stored at 40°C ±2°C /75±5%RH for one month. The blend was evaluated after one month for changes like caking, liquefaction, discoloration and odor formation and by IR spectra. The drug excipient compatibility studies as shown in Table 4.

Table 4: Samples of Rivaroxaban and Different Excipients for Compatibility Studies.

No	Component(s)	Amount(5mg:5mg)
1	Rivaroxaban	1
2	Rivaroxaban and Avicel 102	(1:1)
3	Rivaroxaban and SSG	(1:1)
4	Rivaroxaban and SLS	(1:1)
5	Rivaroxaban and Crospovidone	(1:1)
6	Rivaroxaban and Talc	(1:1)
7	Rivaroxaban and Vanilla Flavor	(1:1)
8	Rivaroxaban and Saccharin Sodium	(1:1)
9	Rivaroxaban and Aspartame	(1:1)
10	Rivaroxaban and CCS	(1:1)
11	Rivaroxaban and Mannitol	(1:1)
12	Rivaroxaban and Mg. Stearate	(1:1)
13	Rivaroxaban and PVP K30	(1:1)
14	Rivaroxaban and Aerosil	(1:1)

Mixing and Compression Processes

Mixing was performed Geometrically, in which all excipients were accurately weighed then all of them with the exception of Aerosil, magnesium stearate and Vanilla flavor, were blended with specified quantity of Rivaroxaban for 15minutes, while the other excipients were blended for 5 minutes and added to the former excipients. Then all formulae were passed through sieve no.18 to achieve particle size uniformity. Then each blend was subjected to powder properties examination and that will be shown in the evaluation of precompression parameters section. Finally, each mixture of each formula has been compressed directly into tablets using rotary tablet compression machine of punch size 6.25mm (7mm chamber diameter) to prepare tablets weighing 130 mg. As shown in Table 5.

Table 5: Composition of Rivaroxaban Formulations ODTs.

Ingredients	Quantity Per Tablet (mg)					
	Formula Code					
	F1	F2	F3	F4	F5	F6
Rivaroxaban	2.5	2.5	2.5	2.5	2.5	2.5
Crospovidone	-	10	10	-	5	-
Sodium Starch Glycolate	5	-	5	10	10	7.5
Croscarmellose Sodium	10	5	-	5	-	7.5
Avicel 102	51.5	51.5	51.5	51.5	51.5	51.5
Mannitol	48	48	48	48	48	48
PVP K30	4	4	4	4	4	4
Sodium Lauryl Sulfate	1.5	1.5	1.5	1.5	1.5	1.5

Aerosil	1	1	1	1	1	1
Magnesium Stearate	0.5	0.5	0.5	1	1	1
Talc	1	1	1	0.5	0.5	0.5
Aspartame	2	2	2	2	2	2
Saccharin Sodium	1	1	1	1	1	1
Vanilla Flavor	2	2	2	2	2	2

Pre-Compression Evaluation of The Powder
Micrometric Properties
Angle of Repose (θ)
Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose as shown in Table 6.

$\tan \theta = h / r$
$\theta = \tan^{-1} (h/r)$ Where, θ is the angle of repose, h is the height of pile, r is the radius of the base of pile.

Table 6: Relationship Between Angle of Repose and Flow Properties.

Flow Property	Angle of Repose
Excellent	<25
Good	25-30
Passable	40-30
Very Poor	>40

Bulk Density
Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$LBD = \frac{\text{Weight of the powder (m)}}{\text{Volume of the packing (vo)}}$$

Tapped Density
The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula:
$\rho_t = M / V_t$

Compressibility Index
The compressibility index of the granules was determined by Carr's compressibility index as shown in Table 7.
(%) Carr's Index can be calculated by using the following formula:
Carr's Index (%) = TBD -LBD /TBD x100

Hausner Ratio
Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula:
Hausner ratio = ρ_t / ρ_d

Where ρt is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Table 7: Grading of the Powders for Their Flow Properties According to Carr's Index.

Compressibility Index	Flow Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very Poor
>40	Very Very Poor

RESULTS AND DISCUSSION
Identification Test
There are many of identification tests used in Rivaroxaban identification. We used Melting point, IR spectrum and calibration curve.

Melting Point
Melting point of pure Rivaroxaban was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Rivaroxaban by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath. The rise in temperature was viewed through screen. The temperature at which the drug started melting was recorded. The melting point of Rivaroxaban was identical to reference melting point stated in USP as mentioned in the Table 8.

Table 8: Melting Point of Rivaroxaban.

Material	Specification	Observation
Rivaroxaban	230 °C	230 °C

Calibration Curve of Rivaroxaban

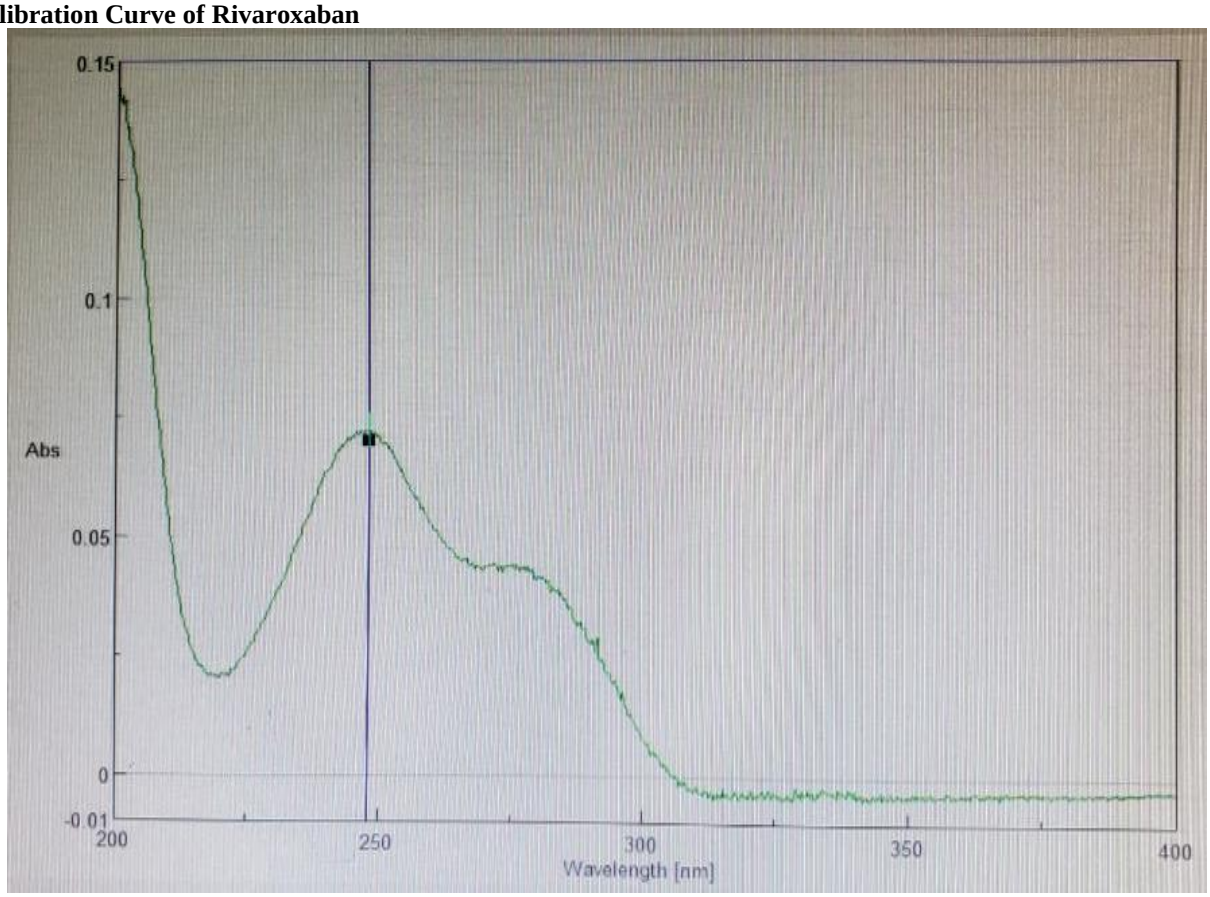


Fig. 1: UV Scanning of Rivaroxaban.

The maximum absorbance of Rivaroxaban in phosphate buffer (pH6.8) was determined by scanning the Rivaroxaban solution from 200-400 nm. The maximum absorbance was found at 248nm. as shown in Figure 1.

Table 9: Calibration Curve of Rivaroxaban in Phosphate Buffer at pH 6.8.

No. Samples	Concentration mcg/ml	Absorbance
1	0	0
2	2	0.0579
3	4	0.1249
4	6	0.1901
5	8	0.2602
6	10	0.3294

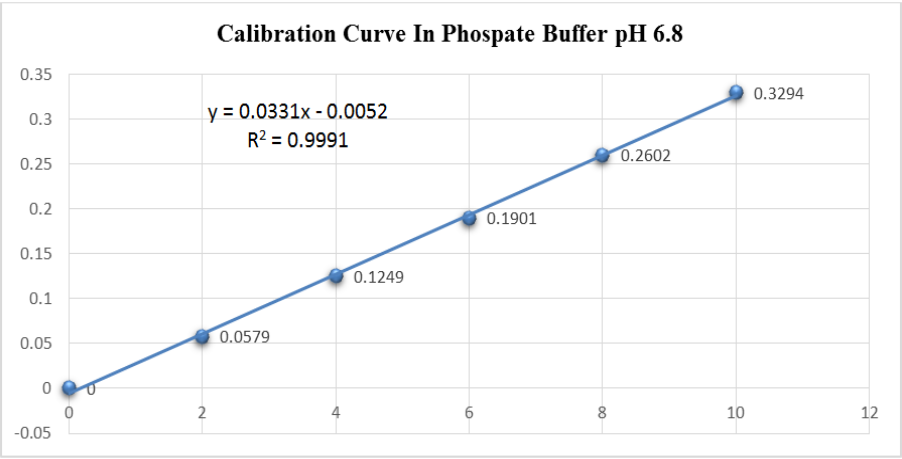


Fig. 2: Calibration Curve of Rivaroxaban in Phosphate Buffer pH (6.8).

The calibration curve of Rivaroxaban was prepared in phosphate buffer (pH 6.8). The plot of different concentrations of Rivaroxaban versus absorbance was found linear at 248 nm in calibrations. The absorbance at different concentrations is shown in Table 9. The regression equation for Rivaroxaban was obtained by plotting absorbance (A) versus concentration of Rivaroxaban (C). The data of standard curve was linearly regressed. The linear regression equation was Y = 0.0331C - 0.0052. The regression coefficient (R2 = 0.9991) was very much significant. The calibration curve was shown in Figure *2*.

Preformulation Tests of Powder

Organoleptic Properties

The organoleptic properties of Rivaroxaban were shown in Table 10.

Table 10: Organoleptic Properties of Rivaroxaban.

Tests	Specification	Observation
Color	Non-hygroscopic, White to Yellowish Powder	Non-hygroscopic, White to Yellow Powder
Odor	Odorless	Odorless
Taste	Bitter	Bitter

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Rivaroxaban was found to be a white to yellow powder, no characteristic odor was observed in the study and the taste was found to be bitter. Rivaroxaban showed similar color, taste and odor as per IP specification as shown in Table 10.

Characterization of Rivaroxaban by FTIR

FT-IR spectral studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Rivaroxaban, thus conforming that no interaction of drug occurred with the components of the formulation excipients as shown in Figures (3-18) and Tables (11-25).

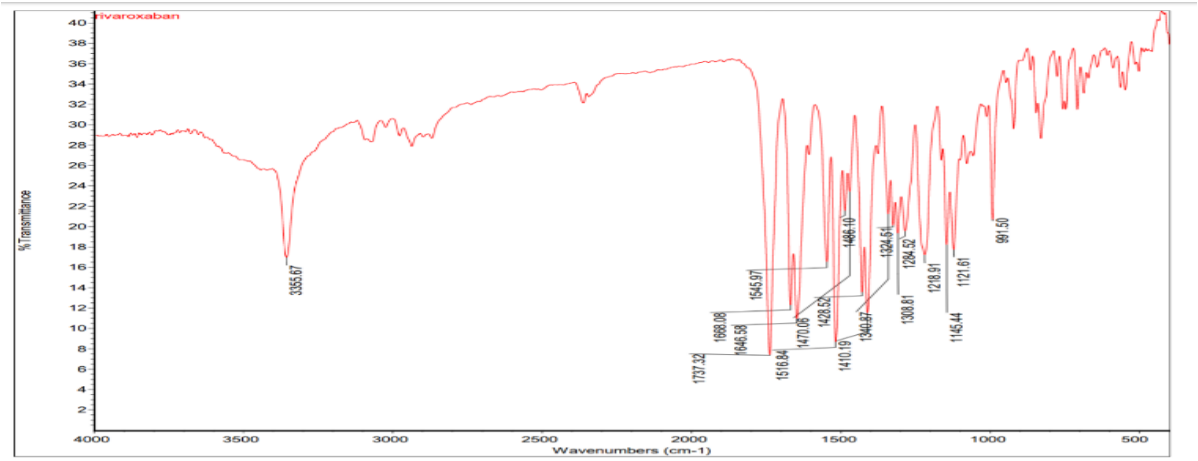


Fig. 3: FTIR Spectrum of Pure Rivaroxaban.

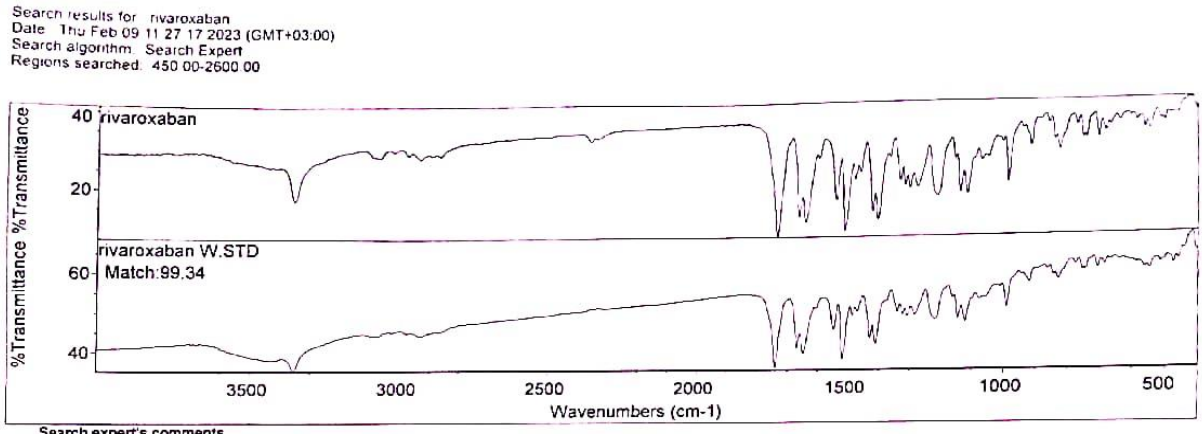


Fig. 4: FTIR Spectrum of Pure Rivaroxaban with STD.

Table 11: Results of IR Spectra Studies.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample ST	1737.32	1668.08	1545.97	1218.91	1121.61	991.50

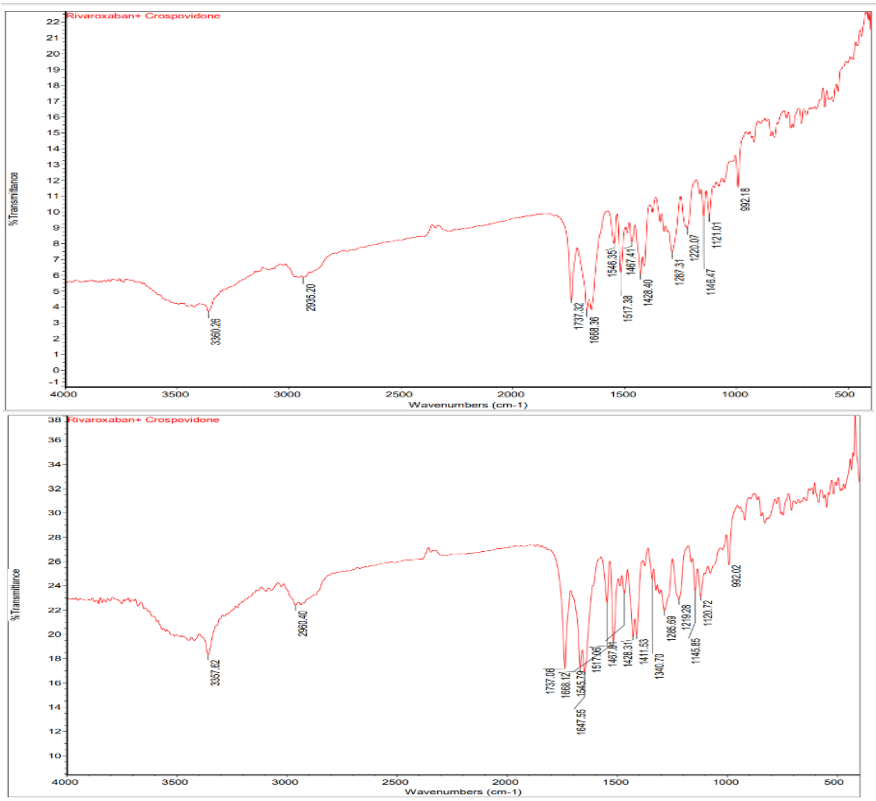
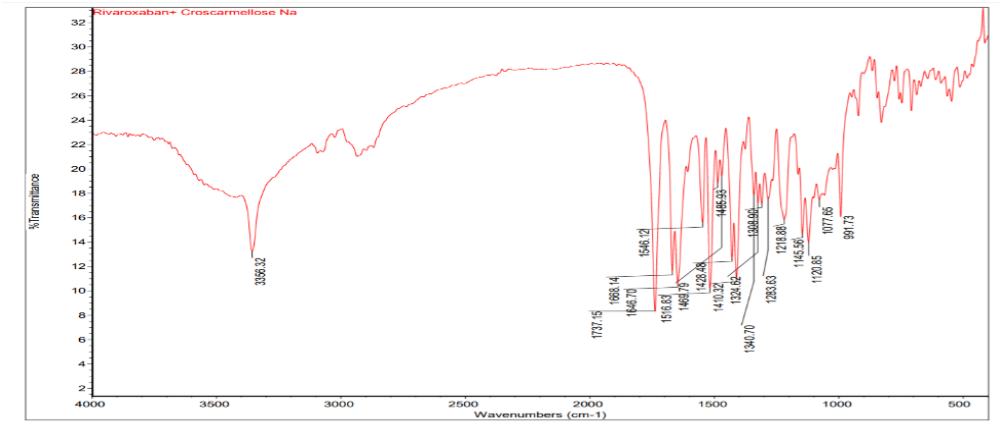


Fig. 5: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Crospovidone.

Table 12: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Crospovidone.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Crospovidone	1737.32	1668.36	1546.35	1220.07	1121.01	992.18
After Stored	1737.06	1668.12	1545.79	1219.28	1120.72	992.02



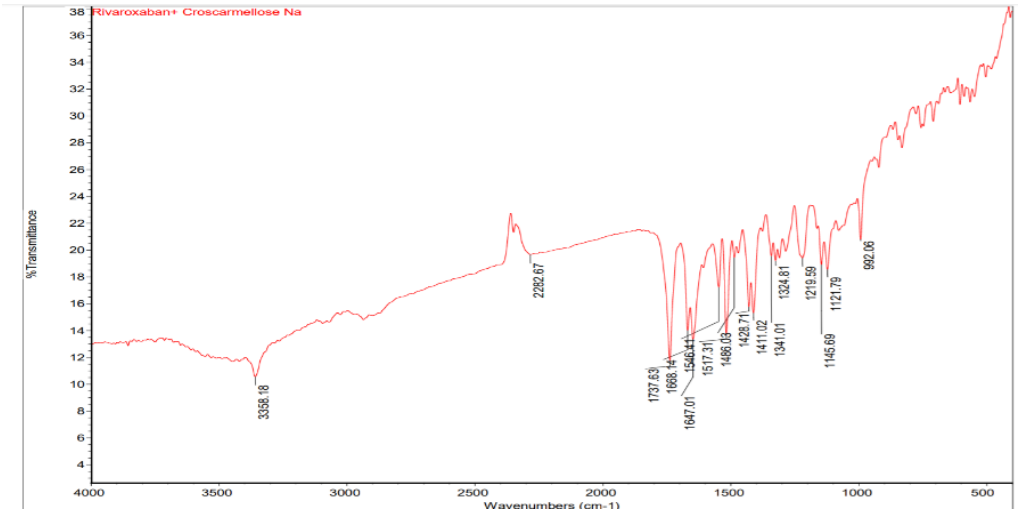


Fig. 6: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and CCS.

Table 13: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and CCS.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with CCS	1737.63	1668.14	1546.41	1219.59	1121.79	992.06
After Stored	1737.15	1668.09	1546.12	1218.86	1120.85	991.73

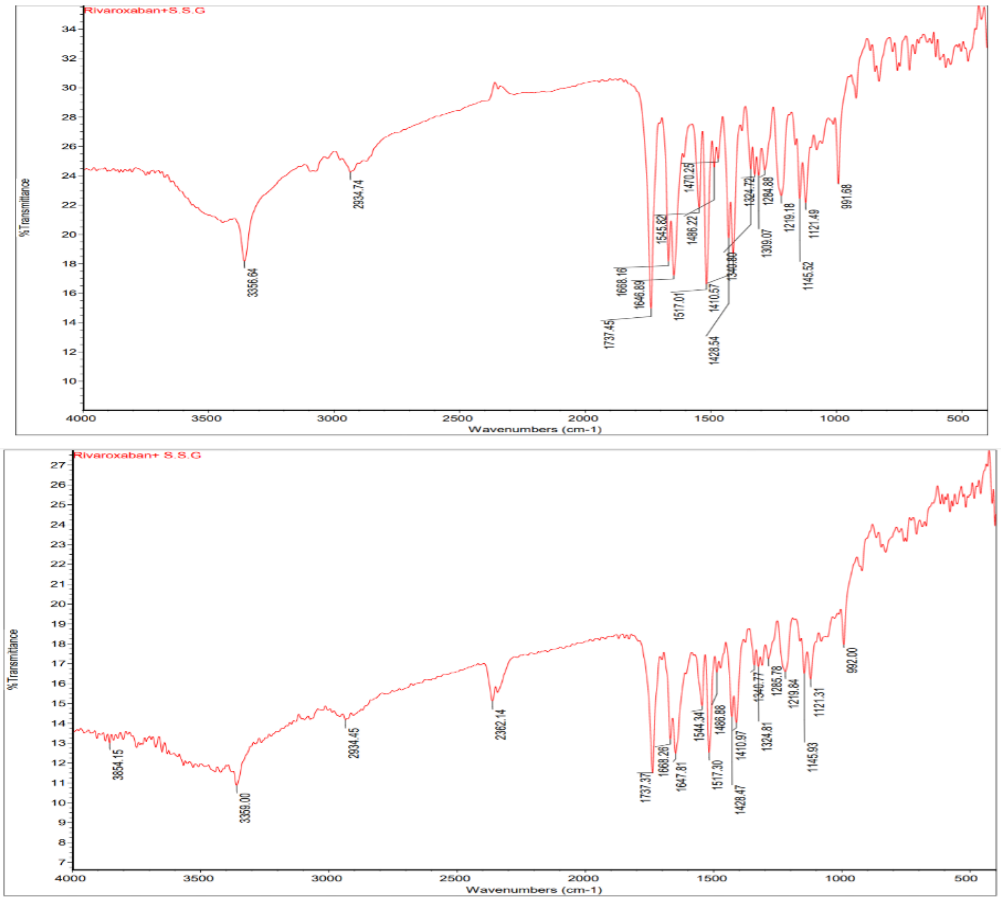


Fig. 7: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and SSG.

Table 14: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and SSG.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with SSG	1737.45	1668.16	1545.82	1219.18	1121.49	991.68
After Stored	1737.37	1668.26	1544.34	1219.84	1121.31	992.00

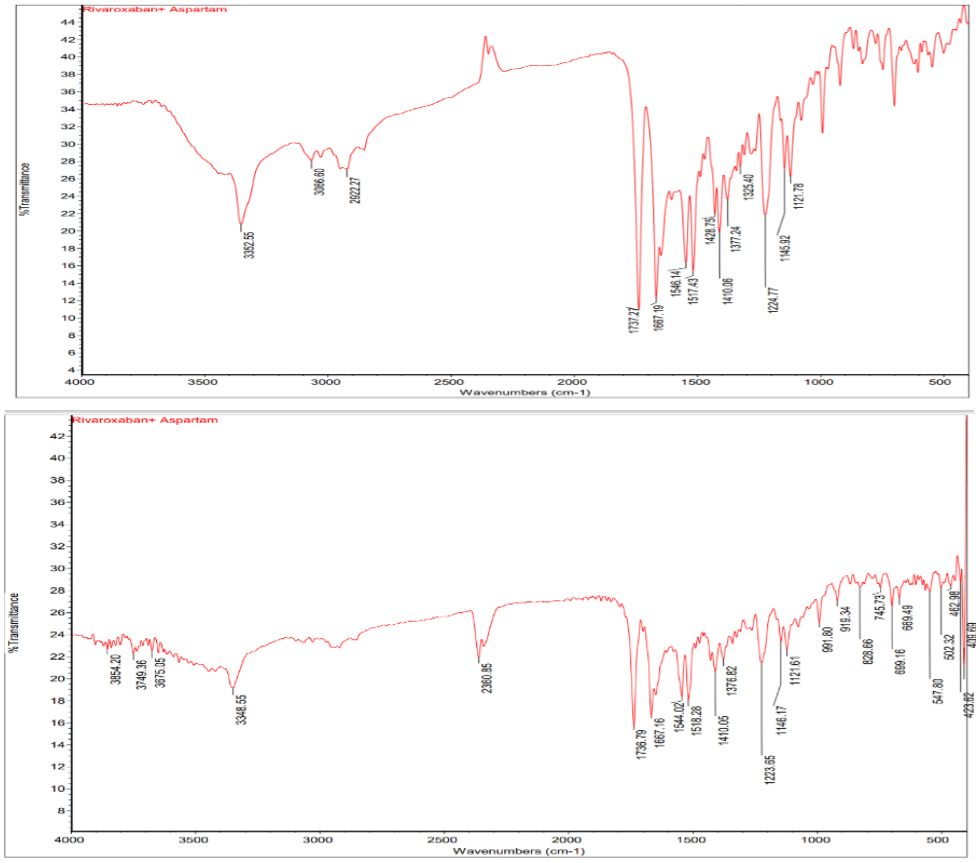


Fig. 8: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Aspartame.

Table 15: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Aspartame.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Aspartame	1737.27	-1667.19	1546.14	1224.77	1121.78	----
After Stored	1736.79	1667.16	1544.02	1223.65	1121.61	991.80

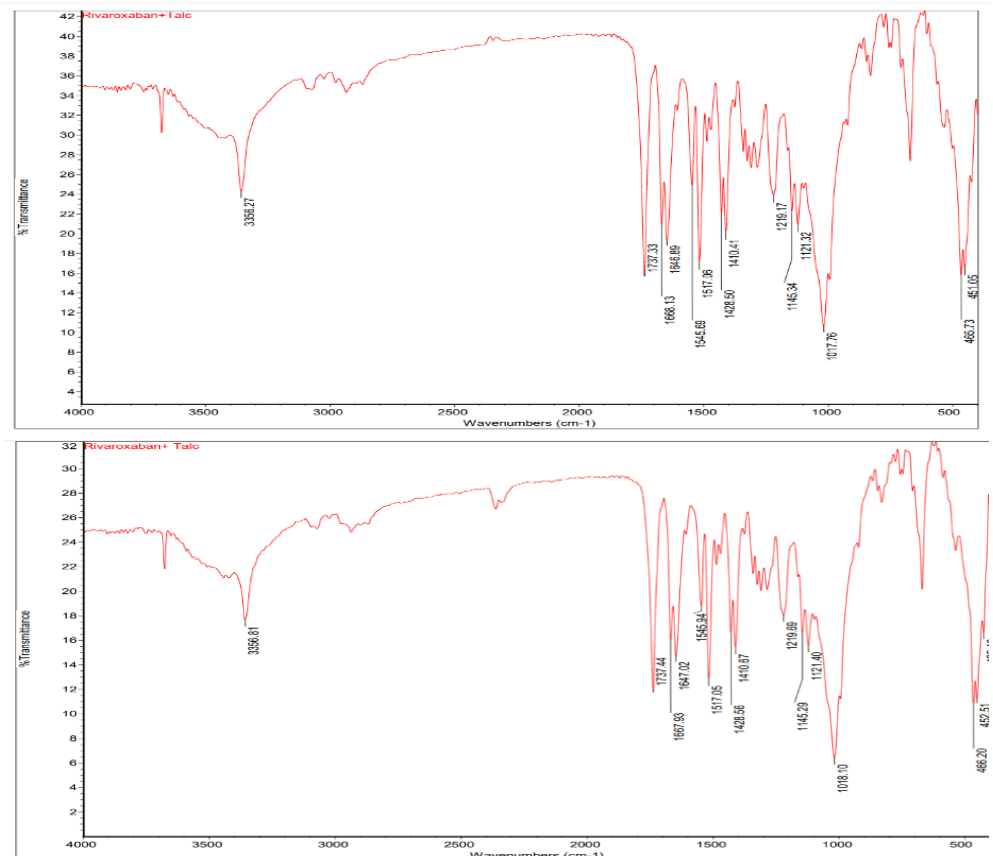
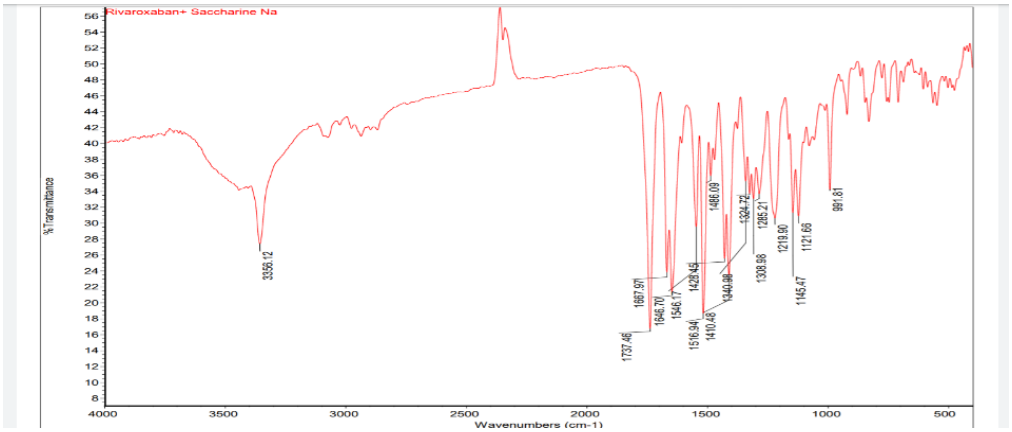


Fig. 9: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Talc.

Table 16: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Talc.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Talc	1737.33	1668,13	1545.69	1219.17	1121.32	1017.76
After Stored	1737.44	1667.93	1545.94	1219.69	1121.40	1018.10



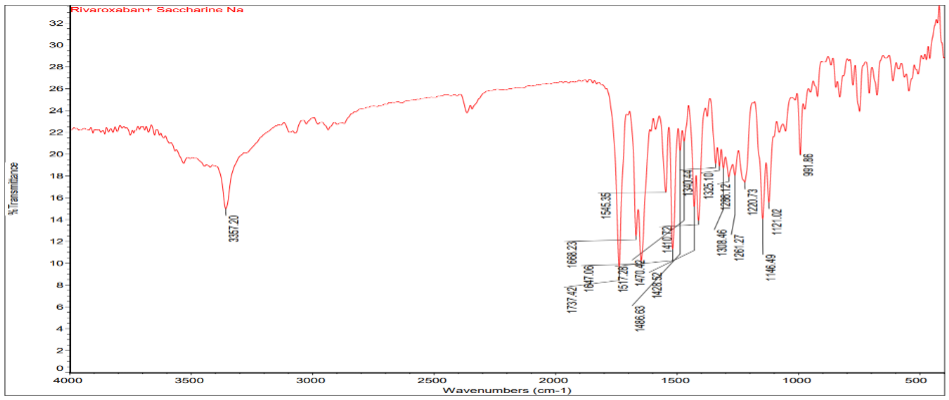


Fig. 10: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Saccharin Sodium.

Table 17: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Saccharin Sodium.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Saccharin Sodium	1737.46	1667.97	1546.17	1219.90	1121.66	991.81
After Stored	1737.42	1668.23	1545.35	1220.73	1121.02	991.86

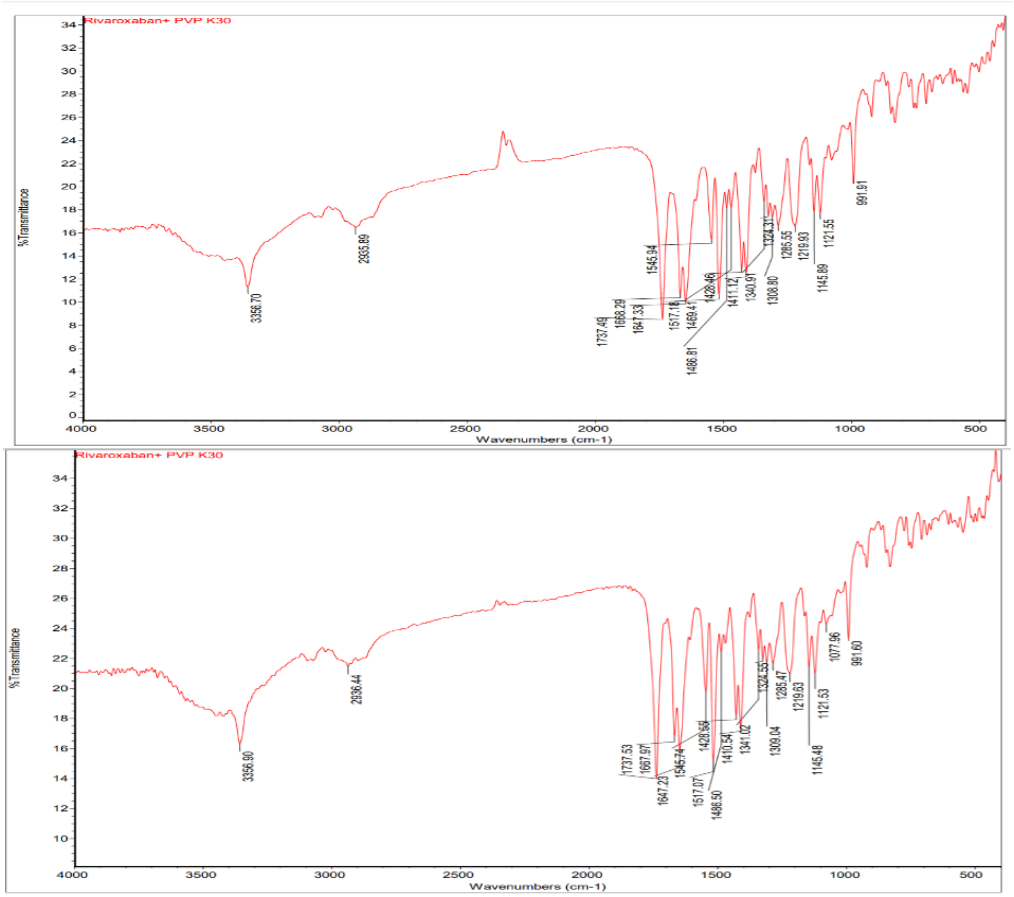


Fig. 11: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and PVP K30.

Table 18: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and PVP K30.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with PVP K30	1737.49	1668.29	1545.94	1219.93	1121.55	991.91
After Stored	1737.53	1667.97	1545.74	1210.63	1121.53	991.60

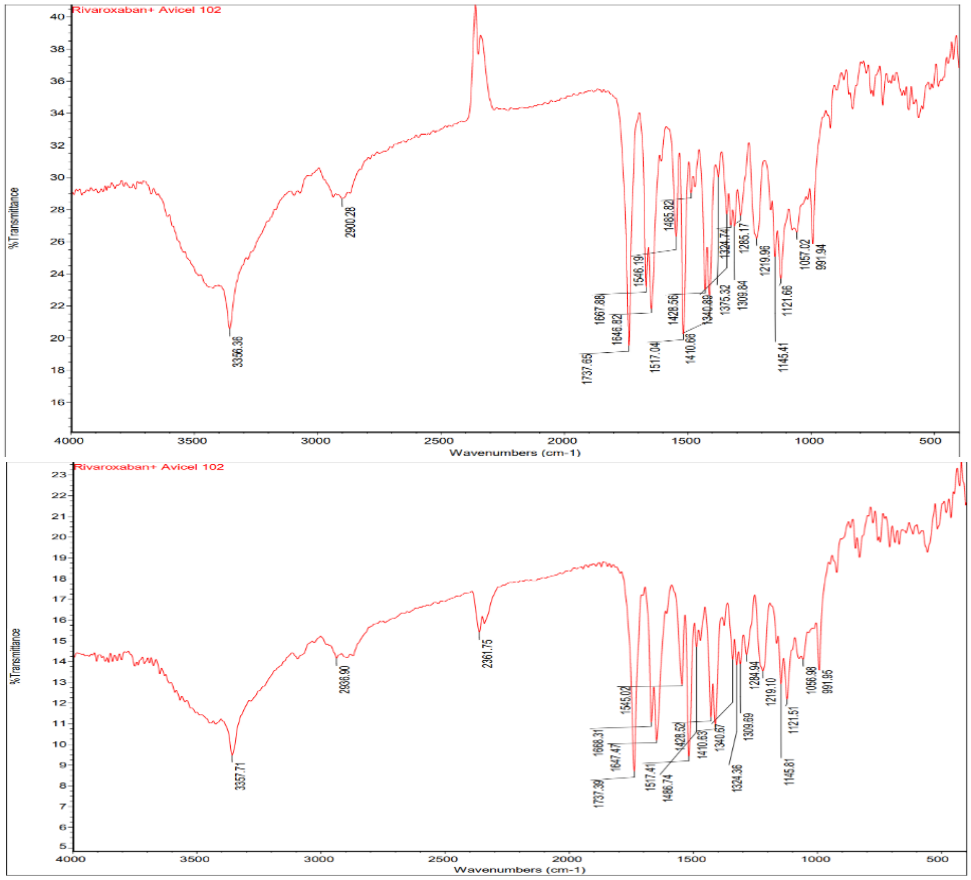


Fig. 12: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Avicel 102.

Table 19: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Avicel 102.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Avicel 102	1737.65	1667.88	1546.19	1219.69	1121.66	991.94
After Stored	1737.39	1668.31	1545.02	1219.10	1121.51	991.95

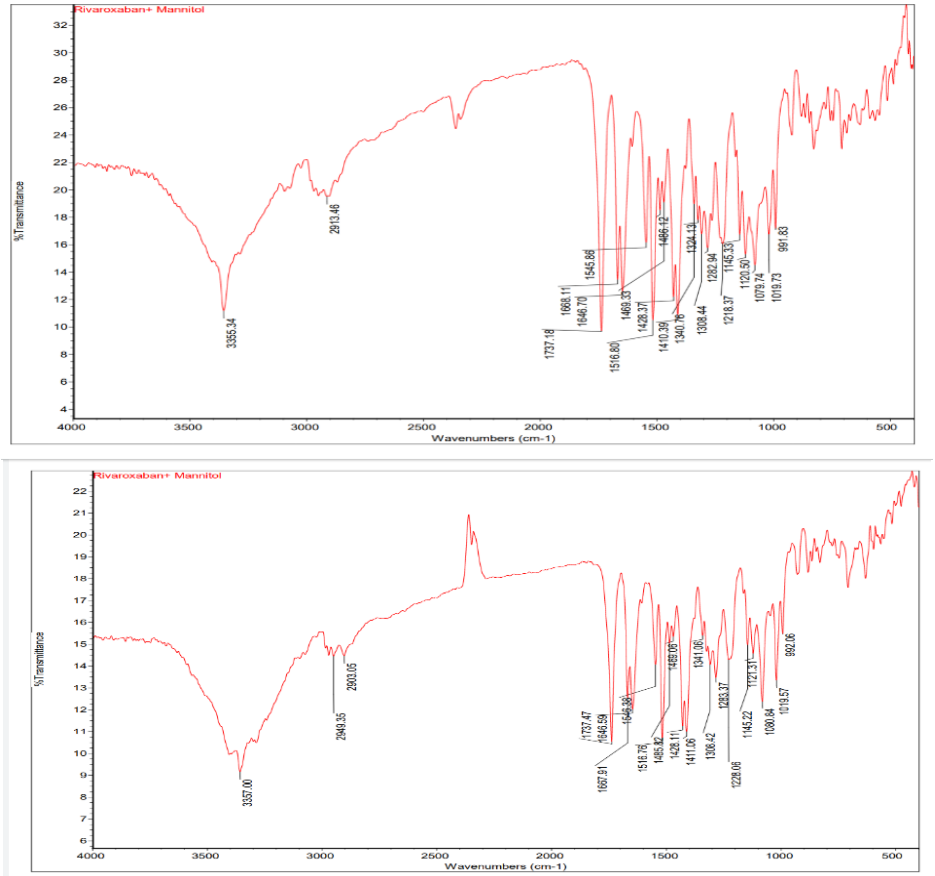
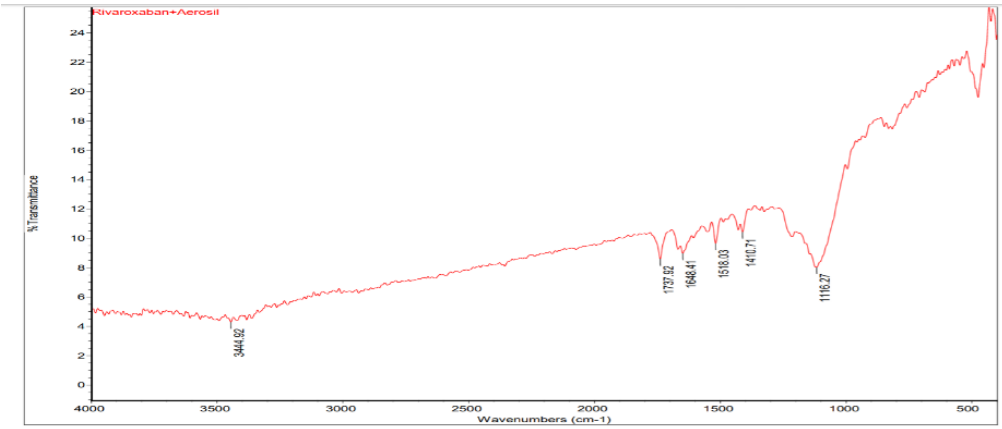


Fig. 13: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Mannitol.

Table 20: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Mannitol.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Mannitol	1737.47	1667.91	1546.38	1218.06	1121.31	992.06
After Stored	1737.18	1668.11	1545.86	1218.37	1120.50	991.83



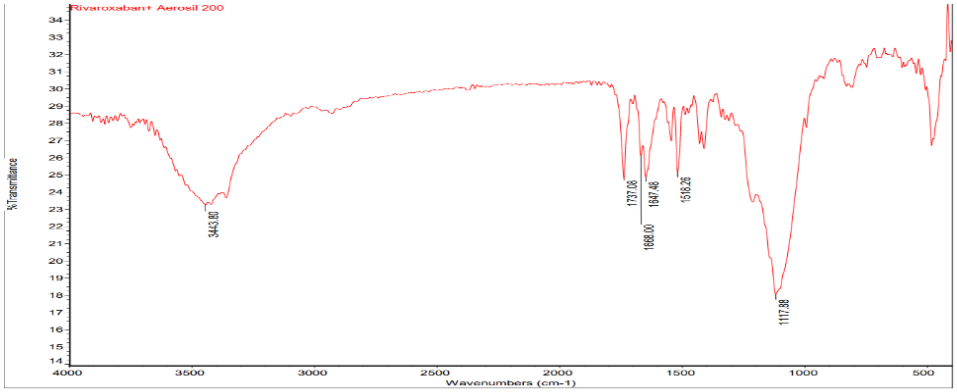


Fig. 14: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Aerosil.

Table 21: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Aerosil.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Aerosil	1737.92	1648.41	1518.03	—	1116.27	—
After Stored	1737.08	1668.00	1518.26	—	1117.88	—

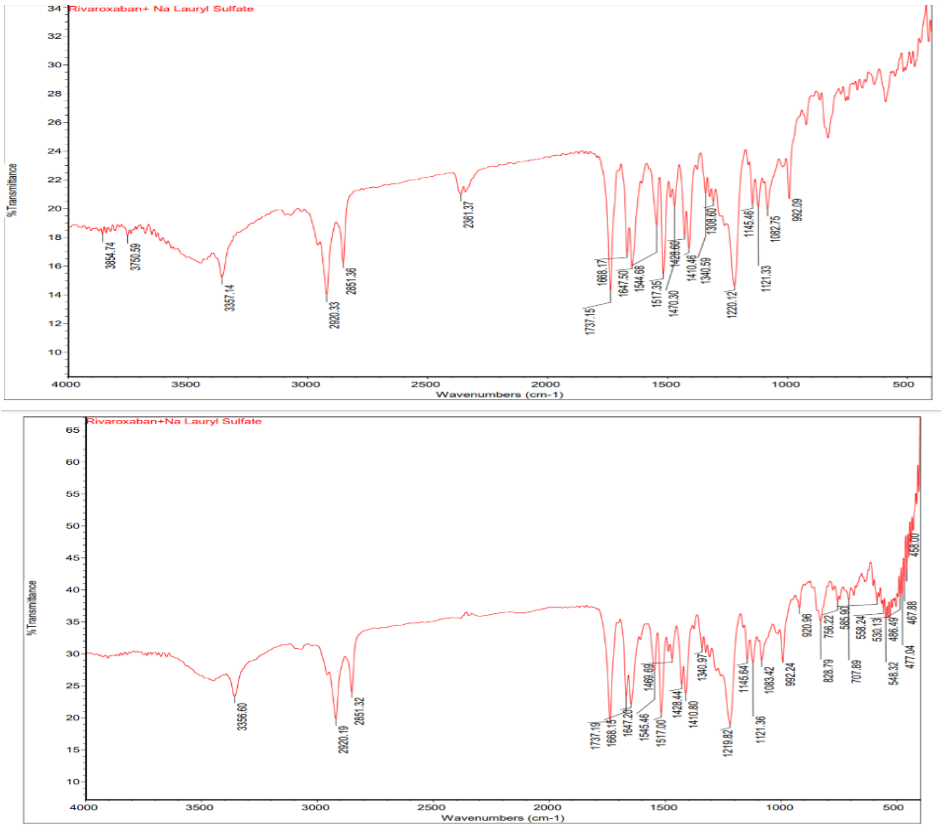


Fig. 15: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and SLS.

Table 22: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and SLS.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50

Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with SLS	1737.19	1668.15	1545.46	1219.82	1121.36	992.24
After Stored	1737.15	1668.17	1544.68	1220.12	1121.33	992.09

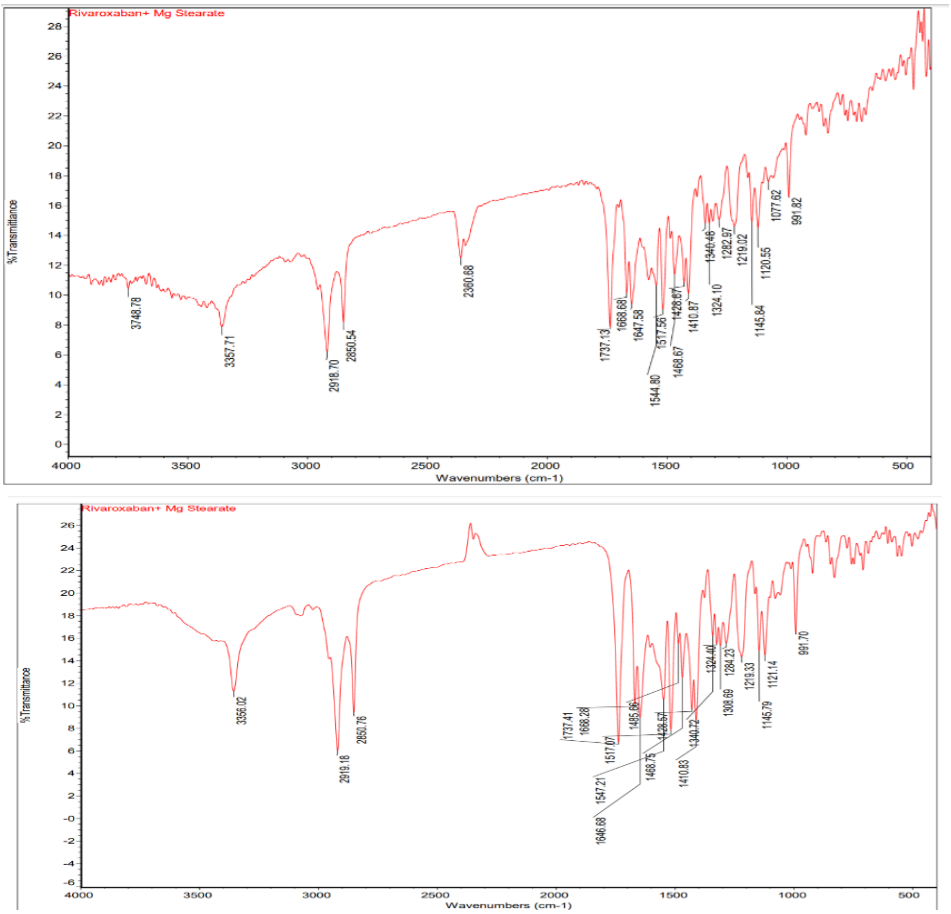
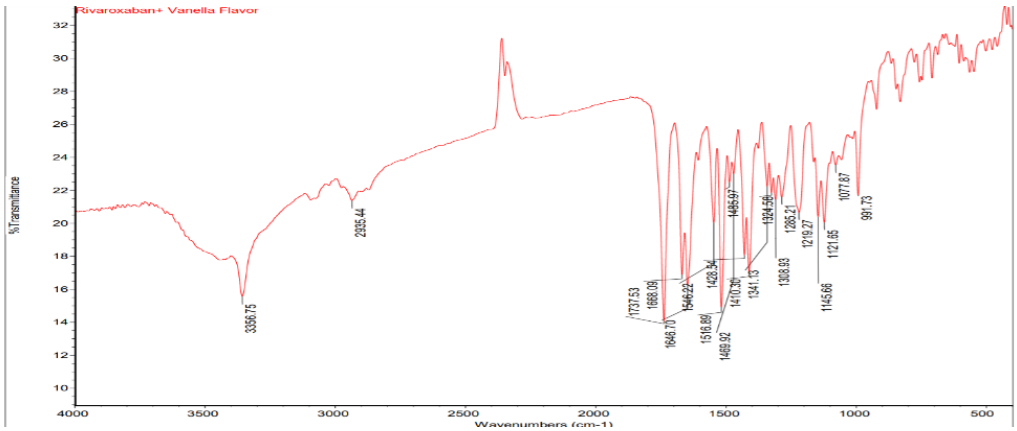


Fig. 16: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Mg. Stearate.

Table 23: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Mg. Stearate.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Mg. Stearate	1737.41	1668.28	1547.21	1219.33	1121.14	991.70
After Stored	1737.13	1668.68	1544.80	1219.02	1120.55	991.82



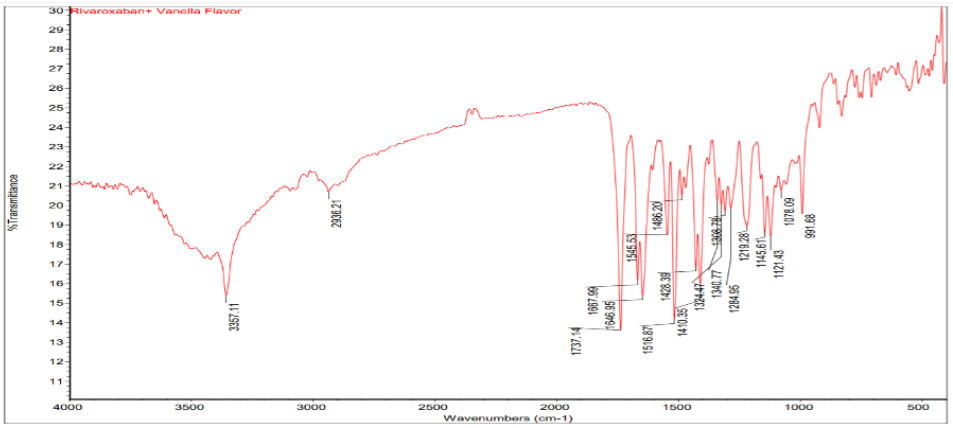


Fig. 17: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Vanilla Flavor.

Table 24: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and Vanilla Flavor.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50
Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with Vanilla Flavor	1737.53	1668.09	1546.22	1219.27	1121.65	991.73
After Stored	1737.14	1667.99	1545.53	1219.28	1121.43	991.68

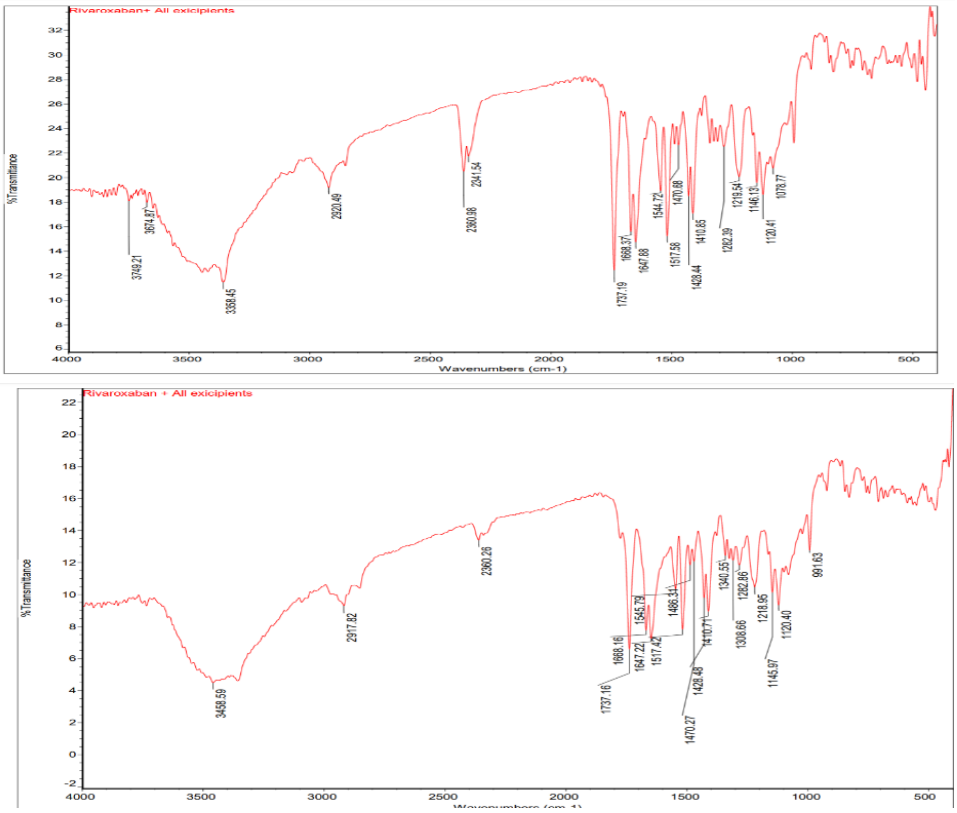


Fig. 18: FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and All Excipients.

Table 25: Results of FTIR Spectrum of Physical Mixture Fresh and Stored of Rivaroxaban and All Excipients.

Specific Functional Groups	Carbonyl C=O Stretching	Amide C=O Stretching	Aromatic C=C Stretching	C-N Stretching	S=O Stretching	C-H Bending
The Mid-IR Region (cm^{-1})	**Around 1730**	**1640-1680**	**1500-1600**	**1200-1350**	**1000-1150**	**800-1500**
Pure Drug STD	1737.44	1668.09	1545.83	1218.98	1121.72	991.50

Rivaroxaban Sample Test	1737.32	1668.08	1545.97	1218.91	1121.61	991.50
Rivaroxaban ST with All Excipients	1737.16	1668.16	1545.79	1218.95	1120.40	991.63
After Stored	1737.19	1668.37	1544.72	1219.54	1120.41	1078.77

Micrometric Properties of Rivaroxaban

The powder of Rivaroxaban was evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The results are given in Table 26.

Table 26: Micrometric Properties of Rivaroxaban.

Raw Material	Bulk Vol	Tapp Vol	Bulk D (g/ml)	Tapp D(g/ml)	Bulkiness
Rivaroxaban	12ml	5ml	0.231	0.5546	4.33
Raw Material	**Voids**	**Porosity (%)**	**Compressibility Index (%)**	**Hausner Ratio**	**Angle of Repose(θ)**
Rivaroxaban	0.583	58.33%	58.34%	2.3982	44.33

The Angle of repose of Rivaroxaban was found to be 44.33%, which indicated Passable –may hang up flow property. The bulk density was found to be 0.231 (g/ml), the tapped density was found to be 0.5546(g/ml). The compressibility index was found to be 58.34% which indicates very, very poor flowability. The hausner ratio was found to be 2.3982.

Evaluation of Precompression Parameter

Micromeritic Properties

Table 27: Evaluation of Precompression Parameters of Rivaroxaban Powder Blend.

Formulation Code	Angle of Repose (ɵ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner Ratio	Evaluation of Angle of Repose
F1	36.027	0.418	0.570	26.66	1.36	Fair
F2	35.93	0.370	0.481	23.07	1.3	Good
F3	33.514	0.370	0.510	27.45	1.37	Good
F4	36.86	0.408	0.572	28.67	1.40	Fair
F5	37.303	0.411	0.548	29.91	1.33	Fair
F6	36.21	0.424	0.530	20.0	1.25	Fair

The angle of repose of formulation 2 and 3 found to be between 33.514 to 35.93 that means its good. The angle of repose of other formulation were found to be between from 36.027 to 37.303, which indicates fair flow properties. The bulk density was found to be between 0.370 to 0.424 g/cm^3. The tapped density was found to be between 0.481 to 0.570 g/cm^3, the compressibility index was found in the range of 20.0 to 29.91% and the hausner ratio lies between 1.25 to 1.40, the results in terms of micromeritics properties revealed that the flow property of formulations F2, F3 were good and other formulations were fair as shown in Table 27.

CONCLUSION

The compatibility studies of physical mixtures of Rivaroxaban with different used excipients such as mannitol, microcrystalline cellulose as diluents, and sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants and sodium lauryl sulfate as wetting agent were investigated by FTIR it was detected that there was no variation or minor deviation in the characteristic peaks in FTIR spectroscopy. The Rivaroxaban formulations prepared were evaluated for precompression parameters and powder flow properties which were found to be within limits. It was concluded that the drug Rivaroxaban was found to be compatible with various excipients which were selected for the formulation development of the Rivaroxaban ODTs. Formulation scientist from his experience and knowledge have to significantly in the preformulation study stage and is an important factor in the ADDS (Advanced Drug Delivery Systems) product development process.

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