RESEARCH ARTICLE

Physicochemical Characterization and Reverse Engineering of Reference Market Product for Generic Formulation Development

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ABSTRACT

The present study aimed to carry out reverse engineering of reference innovator product (Xarelto® 20 mg film-coated tablets) to decode the critical scientific information that is needed for successfully develop a stable and bio-equivalent generic formulation of rivaroxaban 20 mg film-coated tablets. The innovator product characterization was done followed by deformulation of the reference product (Xarelto® 20 mg film-coated tablets) to quantity critical excipients to decode the innovator product's quantitative composition and to identify the manufacturing process used to manufacture the innovator product. The particle size distribution and particle size distribution of rivaroxaban API used in the innovator product were performed using hot-stage microscopy. The polymorphic form of rivaroxaban API used was identified using DSC and XRD methods. Visual, tactile and microscopic evaluation of granules obtained from crushed tablets of the innovator product revealed that the granulation process was used in the manufacturing of the innovator product. It was further concluded that the manufacturing process is wet granulation process due to the presence of organic solvent in the innovator core tablet. Physical evaluation was done to know the tablet weight, shape, size, coating appearance, tablet hardness and disintegration time. Chemical analysis was performed to record the drug content, percentage impurity and dissolution profile. The decoded information can serve as a reference for a faster and bioequivalent generic formulation development with reduced cost, time, effort, and a higher success rate.

Keywords: Rivaroxabán, Generic, Reverse engineering, Xarelto®, Reference innovator product.

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INTRODUCTION

Generic products are essential in healthcare systems worldwide due to their numerous benefits. Firstly, they offer cost savings by being more affordable compared to brand-name drugs. This affordability expands access to medications, particularly for individuals with financial constraints.[1] Additionally, the presence of generic products fosters competition in the pharmaceutical market, leading to lower prices and increased innovation. Generic products provide therapeutic alternatives, ensuring equivalent effectiveness and safety compared to brand-name drugs. They contribute to the sustainability of healthcare systems by reducing medication costs and optimizing resource allocation.[2] Moreover, generic products expand treatment options, allowing healthcare providers to choose medications based on individual patient needs. Globally, generic products play a vital role in improving public health by enhancing access to affordable medications, particularly in developing countries.[3]

The development of generic drug products is a highly competitive and challenging process that requires significant effort and carries inherent risks. The primary objective is to achieve pharmaceutical equivalence with the innovator's drug product.[4] However, the successful development of a generic product can yield substantial financial rewards and a strong return on investment for the investor. Moreover, it expands the availability of affordable healthcare options for the patient population, enhancing accessibility. Throughout the entire pharmaceutical development process, from formulation development to manufacturing and quality control, developers strive to optimize efficiency while upholding stringent standards of quality and safety. This involves careful attention to detail and a focus on maintaining high standards at every stage of development.[5] The development of generic products typically starts with the characterization of the innovator product or reference-listed drug (RLD). This process involves analyzing various aspects of the RLD, such as its quantitative

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formula, release profile (for solid oral dosage forms), and pH/viscosity (for liquid oral formulations).[6] Conducting a systematic and scientific review of the RLD provides essential information, often referred to as de-formulation studies, that guides the development of the generic product. These studies help acquire crucial knowledge about the RLD, aiding in the development of a comparable generic formulation.[7]

Reverse engineering studies are a systematic approach used to characterize the innovator drug product. Through reverse engineering, researchers aim to gather essential information regarding the qualitative, quantitative, and structural aspects of the product components.[8] This includes a focus on the active ingredient (the drug or active pharmaceutical ingredient) as well as other pharmacologically inactive ingredients present in the product formulation. By conducting these studies, a comprehensive understanding of the innovator drug product can be obtained, facilitating the development of comparable generic formulations. The process of decoding the RLD starts by identifying the excipients used in the formulation. It is important to also identify the excipients that have an impact on the formulation's performance, specifically in terms of quality tests such as stability and dissolution.[6] Analyzing this data helps determine the resources required for reverse engineering and assess the value of the information obtained. Among the excipients, disintegrants, lubricants, diluents, surface-active agents, and binders are often the most suitable candidates for reverse engineering studies. By focusing on these key excipients, researchers can gain valuable insights into the formulation and optimize the reverse engineering process effectively.[9] The utilization of reverse engineering tools enables faster, cost-effective, and scientifically-driven development of generic products. It serves as a crucial factor in designing and developing innovative and improved drug products.[10] By leveraging reverse engineering, the availability of generic drug products in the market can be enhanced, providing wider access to affordable medications. This approach not only supports the development of generics but also contributes to the advancement of pharmaceutical innovation, leading to the creation of better drug products for improved healthcare outcomes.[11]

The primary goal of the study was to reverse engineer the reference market product, Xarelto® 20 mg film-coated tablets and thus to generate base data from the decoded information. This can serve as reference data in order to develop a robust and stable generic formulation of Rivaroxaban 20 mg film-coated tablets, which will be bioequivalent and closely resembling with the reference market product, Xarelto® 20 mg film-coated tablets a concise summary of the physicochemical characterization and reverse engineering studies is provided.

MATERIALS AND METHODS

Materials

The reference market product, Xarelto® 20 mg film-coated tablets was purchased from a local pharmacy. Rivaroxaban API was obtained as a gift sample from Mylan Laboratories, India, Croscarmellose sodium was from DFE pharma, Magnesium stearate was from Merck, and sodium lauryl sulfate was from BASF. All the chemicals and reagents used in the analysis were of analytical grade. Milli Q water was used for analysis.

Reverse Engineering of Reference Product

Physicochemical characterization of RLD

The characterization of Xarelto® 20 mg film-coated tablets RLD was performed in which tablet weight, hardness, thickness, disintegration time, shape, diameter, assay, and dissolution were determined as per the standard procedures reported in the literature.

Characterization of Reference Innovator tablets

Tablet weight and weight variation

To determine the weight variation, the official procedure was followed as per USP. A total of 20 reference product tablets were selected, and their weights were measured with precision balance, and recorded in mg. The mean tablet weight and standard deviations were then calculated based on the collected data.

Thickness

To determine the thickness of tablets, a digital vernier caliper (Mitutoyo, Japan) was utilized. A total of 10 tablets were chosen at random for this test. The dimensions of the tablets were measured and recorded in mm.

Hardness

To assess the hardness of the tablets, an automatic hardness tester (TH - 1050M, Labindia, India) was employed. A total of 10 tablets were selected for this measurement. The hardness of each tablet was measured individually, and the values were recorded. The average hardness value, as well as the standard deviation, were calculated using the collected data.

Disintegration test

The disintegration test was performed on six tablets using a disintegration test apparatus (DT 1000, Labindia, India). A disintegration medium consisting of distilled water at a temperature of 37 ± 0.5°C was used. The time required for the reference product tablet to completely disintegrate, with no detectable mass remaining in the apparatus, was measured in seconds.

Friability

In this particular test, a total of 20 tablets were selected after carefully scrapping off the coat. These tablets were subjected to 100 rotations using an automatic friability ((FT - 1020, Labindia, India). The weight of the tablets, after the removal of dust, was carefully measured and recorded. The friability of the tablets was then determined by calculating the mean of three separate determinations. Typically, tablets with a weight loss of less than 1% were considered suitable for use.

Assay (Drug content)

An assay test was performed to record the rivaroxaban content of the reference product tablets using the reverse

phase HPLC method. Tablets were crushed into powder and 92 mg (equivalent to 20 mg of Rivaroxaban) was added to the mobile phase and sonicated for 30 minutes and filtered with 0.45 µ filter and then injected. An HPLC system (Agilent 1260 Infinity II) with Openlab EZ Chrome) with UV detector used with chromatographic conditions of Column: C18, 100 x 4.6 mm, 5 µ (Waters, USA), Mobile phase: Acetonitrile: Water 40:60% v/v, Isocratic elution, Flow rate: 1-mL/min, Column oven temperature: 40°C, Wavelength: 250 nm, Injection volume: 10 µL.

In-vitro release studies

The dissolution test was conducted using a USP type II dissolution test apparatus (TDT-06P, Electrolab, India) to evaluate the release of rivaroxaban from the reference market product, Xarelto® 20 mg film-coated tablets. The test involved using a pH 4.5 acetate buffer with 0.4% sodium lauryl sulfate (900 mL) at a temperature of 37°C ± 0.5°C. The apparatus was operated at a rotation speed of 75 rpm. During the test, samples of 5 mL were withdrawn at predetermined time intervals (5,10, 15, 20, 30 and 45 minutes) and immediately replenished with an equal volume of freshly prepared buffer to maintain sink conditions. These samples were then filtered through 0.45 µm filters to obtain clear solutions, and the drug content was determined using HPLC method described for drug content using UV detector at a wavelength of 250 nm (USP).

Determination of qualitative formula and excipients

The qualitative formula of the reference tablets was obtained from PIL (Patient Information Leaflet) and the excipients used in the core tablets of the reference product were reported. Table 1 evaluated the risk and need of quantification based the qualitative composition.

Core tablet weight and coating weight gain identification

The coating film of 100 core tablets was very carefully peeled off manually using a surgical blade. The total weight of the coating layer removed tablets was compared with the initial weight of the 100 film-coated tablets. From the difference in weight obtained, the average core tablet weight for a single tablet was calculated. From the weight loss i.e., the difference in weight obtained between the initial film-coated tablets and the weight of the coating layer removed tablets, the coating layer weight was calculated.

API PSD and polymorph identification

API PSD used in the reference product was decoded using hot-stage microscopy.[12] API polymorphic form used in the reference product was identified using the reference standard of API polymorphic form-1 and also by comparing with the melting point reported for polymorphic forms, form-1 and form-2.

XRD and DSC of reference product and API

DSC was performed using a simultaneous thermal analyzer (STA 449 F3 Jupiter, NETZSCH GmbH, Germany) heating range of 10 to 300°C and a heating rate of 10ºC/min. Powder XRD was performed using PANalytical X'pert3, using high score software between 2θ range of 5 to 50.

Critical Excipients Quantification

SLS by titrimetric method

The quantification of SLS was performed by applying an in-house procedure based on the direct titrimetric method. In brief, stock solutions at different known concentrations for linearity are prepared equivalent to 0.9, 1.8, 2.7, 3.6, 4.5, 5.4, 6.3 and 7.2 mg to determine the volume consumed for respective concentrations and a calibration curve is plotted. The sample solution was prepared by weighing 360 mg of finely powdered tablets and diluting them to 100 mL. The prepared stock and samples were sonicated and heated to 50°C for 15 minutes and cooled down before titration. The titration procedure involved 30 mL of supernatant of stock or sample was added with 25 mL of methylene blue and 15 mL of methylene chloride

Table 1: Need for critical excipient quantification from reference tablets and risk identification

Component	*Quantity*	*Functionality*	*Excipient criticality*	*Critical information to be decoded in order to match and achieve equivalent product performance with reference product*
Rivaroxaban API	20MG	Active	---	API particle size and polymorphic form used by Innovator
Lactose monohydrate	21.76	Diluent	Low	Preferable if quantity can be matched
Microcrystalline cellulose (MCC)	Unknown	diluent	Low	Preferable if quantity can be matched
Hypromellose (hydroxypropyl methylcellulose- HPMC)	Unknown	Binder	Moderate	Desirable to match Quantitatively this critical functional excipient as this excipient can influence *in-vitro*/*in-vivo* disintegration pattern .
Sodium lauryl sulphate	Unknown	Solubilizer	High	Quantitatively, to match this critical functional excipient as this excipient can influence *in-vitro*/*in-vivo* solubility and the invivo permeability
Croscarmellose sodium (CCS)	Unknown	Disintegrant	High	Quantitatively, to match this critical functional excipient as this excipient can influence dissolution profiling and *in-vitro*/*in-vivo* drug product performance.
Magnesium stearate	Unknown	Lubricant	Moderate	Desirable to match Quantitatively this critical functional excipient as an excessive amount this excipient can negatively impact disintegration and dissolution behavior and suboptimal concentration of this excipient may impact manufacturing processability.

and 20 mL of purified water, using 0.004M benzathonium chloride as titrant. The endpoint was visually detected when the intensity of the blue color is the same in both layers. The concentration of sodium lauryl sulfate obtained from the titrimetric determination is 1.010 mg, and the SLS quantity was fixed as 1.0 mg per tablet for generic product development.

Quantification of croscarmellose sodium (Sodium content by ICP-MS)

Indirect quantification of croscarmellose sodium was performed through sodium content determination using ICP-MS (Agilent 7800). Calibration Curve was prepared in a range of 0.5 to 4 µg/mL for sodium **(**Figure 1**)**. In 40 mg of powdered reference product tablet was dissolved in 10 mL, 65% nitric acid and subjected to Microwave digestion followed by dilution with Milli Q water. Dissolved 1-mL of the digested solution into the 9 mL of Milli Q water to get the final clear solution and then analyzed.

Quantification of magnesium stearate (Magnesium content by ICP-MS)

Indirect quantification of magnesium stearate was performed through Magnesium content determination using ICP-MS (Agilent 7800). Calibration curve was prepared in a range of 1 to 8 µg/mL for magnesium **(**Figure 2). In 40 mg of powdered reference product tablet was dissolved in 10 mL 65% Nitric acid and subjected to microwave digestion followed by dilution with Milli Q water. Dissolved 1-mL of the digested solution into the 9 mL of milli Q water to get the final clear solution and then analyzed.

Quantification of microcrystalline cellulose

The concentration of MMC was derived by summing up the total quantity of rivaroxaban (20 mg), lactose monohydrate (21.76 mg), hypromellose (1.8 mg), SLS (1-mg), CCS (5.3 mg), magnesium stearate (1.5 mg) i.e., 51.36 mg and then deducting it from the core tablet weight of 90 mg.

Manufacturing Process Identification

Visual appeal and microscopic observation

The reference product samples were added to a beaker containing water, and the dispersion and disintegration pattern was observed visually. Also, a coating film was removed, core tablets of the reference product was gently crushed and the inner core particles were three-dimensionally viewed under magnification using an optical stereo zoom microscope (LUXEO 6Z, Labomed India).

Surface morphology using a scanning electron microscope

Surface morphology of the crushed tablet was studied under a scanning electron microscope (SEM, JSM-IT200, JEOL, Japan).

Tactile evaluation

Physical touch evaluation of gently crushed and the inner core particles was done by holding and rubbing with a rolling motion of little mass between fingers to know if the feeling is gritty or fine and soft.

Solvent content evaluation

Residual organic solvent quantification was carried out using validated headspace gas chromatographic method with a flame ionization detector (FID). The extraction was performed using a headspace sampler with 20 mL vial. Separation was done using the chromatographic conditions, GC Column used was AS-624 MS, 30 m x 0.32 mm, 0.5 µm (30 m length × 0.32 mm ID, 0.5 µm film thickness). Initial oven temperature, 50°C; hold for 5 minutes, and increased to 250°C at the rate of 20°C/min; hold for 10 minutes. Standard solution was prepared by mixing with 1-gm of ethanol in 100 mL of water, and then making to volume to 250 mL with water. Sample solution was prepared by adding 1-g of powdered tablet in 100 mL of water, mixing and then making up the volume to 250 mL with water. The injection volume was 5 µL. The run time of analysis was 20 minutes. The injector and detector temperature was kept at 250 and 280°C, respectively. Nitrogen was used as a carrier gas with a constant pressure. The chromatographic signal (peak area) and calibration curves of the standard organic solvent solution plotted previously made it possible to estimate the concentration of solvent (Figure 3).

Reverse engineering of innovator packaging material

Primary packaging plays a critical role in drug products' stability as they protects the drug product from environmental factors throughout their shelf-life period. The packaging components present in the reference product's packaging material was ascertained by subjecting the packaging material samples to undergo chemical testing, FTIR spectral analysis and physical dimensional measurements.

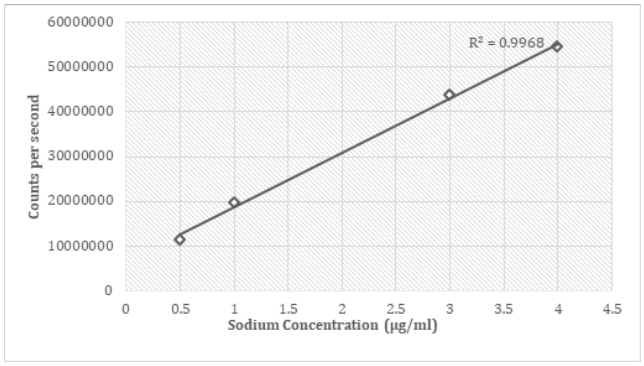

Figure 1: Linearity curve for sodium

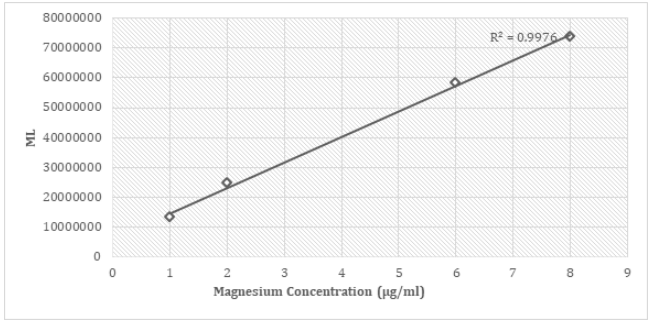

Figure 2: Linearity curve for magnesium

RESULTS AND DISCUSSION

The primary objective of the present study was to perform reverse engineering of the reference innovator product, Xarelto® 20 mg film-coated tablets, marketed as a conventional immediate-release tablet dosage form. Rivaroxaban, being a poorly soluble drug is classified as BCS Class II (poorly soluble and highly permeable), faces challenges in terms of its solubility, which impacts its bioavailability.[13] Therefore, in this case, the goal was to decode the critical scientific information from the reference product so that it may serve as reference data in order to develop a generic product that can match the solubility and dissolution profile across the gastrointestinal pH range to predict and achieve equivalent *in-vivo* performance compared to the reference product.

Characterization of Reference Listed Drug

The detailed RLD characterization of Xarelto® 20 mg film-coated tablets was performed to understand the various aspects of the RLD that would help in the development of generic products. Table 2 summarises the various parameters evaluated for RLD.

Physical characterization

The average weight of the tablets was found between 92.3 mg. All tablets passed the weight variation test with 90.0 mg ± 10.0%. The hardness of the tablets was found in the range of 6.0 to 8.0 Kp which was quite acceptable considering the very low friability value obtained. DT was found well within the official limit of NMT 60 minutes. The results of the evaluated parameters are presented in Table 2.

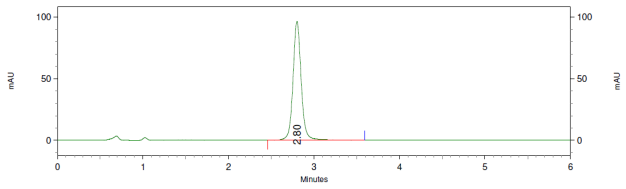

Figure 3: Typical chromatogram of rivaroxaban

Table 2: Characterization of Xarelto® 20 mg film-coated tablets

Reference product characterization	
Generic Name	Rivaroxaban 20 mg tablet
Brand Name	Xarelto
Appearance	Brownish, Appearance round, film-coated tablets
Strength	20 mg tablet
Route of administration	Oral
Primary packing material	Transparent blister
Type of Tablet	Immediate release tablet
Score line	absent
Coating	Present
Assay	100.2%
Weight	92.2 ± 0.4 mg
Tablet shape	Round
Tablet size / Diameter (mm)	6 ± 0.03 mm
Tablet hardness (kp)	6-8 KP
Tablet disintegration time	2–4 minutes

Assay (Drug Content) of reference product tablets

The assay of 10 tablets was found between 99.9 and 100.2. The acceptance limit of between 90.0 to 110.0%.

In-vitro dissolution study

Dissolution profiling of reference product showed a faster drug release profile with a quick disintegration and dispersion pattern. The dissolution behavior of the reference product is depicted in Figure 4.

Qualitative formula and excipients

The qualitative composition of the reference tablets was obtained from the patient information leaflet (PIL). The core tablets of the reference product consist of lactose monohydrate, microcrystalline cellulose, hypromellose (HPMC), sodium lauryl sulfate, croscarmellose sodium, and magnesium stearate. In accordance with the regulations set by the European Medical Agency, specific product characteristics (SPC) disclose quantitative information for excipients with known effects. From the SPC, it was determined that the quantity of lactose (specifically, lactose monohydrate) in each tablet is fixed at 21.76 mg for the development of the generic product.

Core tablet weight and coating weight gain identification

The initial weight of 100 film-coated tablets was found to be 9.202 gm and after peeling the film the weight of 100 core tablets was 8.989 gm. So, the weight of single core tablet was found to be 90 mg and the coating layer weight was calculated as 2.22 mg and fixed for generic product development as 2.0 mg (2.22%).

API PSD and polymorph identification

The hot-stage microscopy (HSM) study was described in our previously published work.[14] Figure 5 shows an image of the reference product under hot melted stage during the HSM analysis. From HSM analysis of the reference product, it was found that D90 of 77 microns. It was decided that average D90 value of API to be used for generic formulation development shall be closer to the D90 value obtained for the API from the reference product analysis. API polymorphic form-1 was used by the reference product and the selected API polymorphic form-1 shall be used for generic product development.

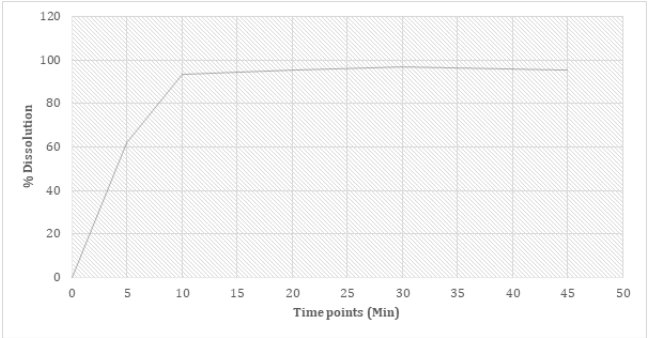

Figure 4: Dissolution profile of reference product in release media

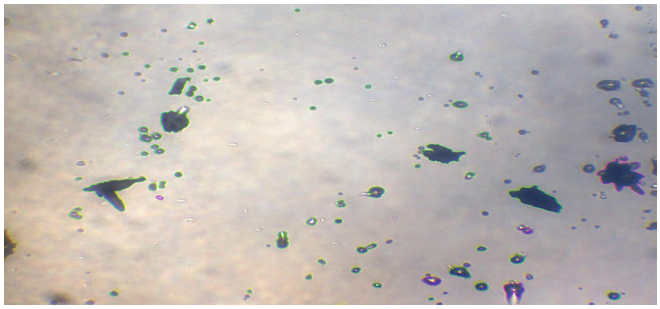

Figure 5: Melted stage captured during the HSM analysis

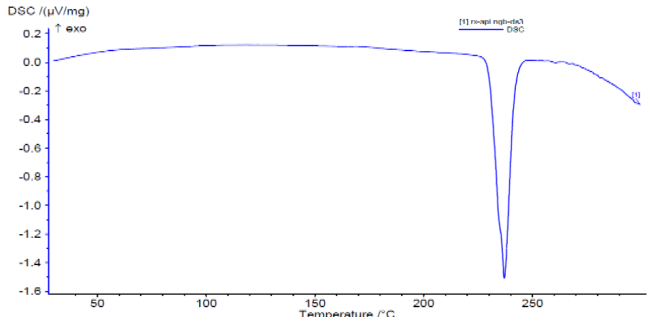

Figure 6: DSC thermogram of Rivaroxaban API Form-I

XRD and DSC of reference product and API

The reported melting point of rivaroxaban form-I was found to be around 230°C **(**Figure 6**)** and form-II was 203°C.[15,16] The DSC thermogram of RLD was also found with an endothermic peak at 230°C as shown in Figure 7. These observations indicated that the innovator product also developed with rivaroxaban form-I. The XRD pattern of rivaroxaban form-I showed clear, sharp, and distinct peaks at 2θ of 16.4676^0, 19.4554^0, 19.8642^0, 22.4597^0, 25.5604^0, and 26.5897^0 (Figure 8). Similar peaks were also reported in the RLD sample at 2θ of 16.3441^0, 19.4201^0, 19.8194^0, 22.3948^0, 25.5292^0, and 26.4318^0 (Figure 9). These observations confirmed the identical nature of rivaroxaban form-I with rivaroxaban used in RLD.

Critical Excipients Quantification

The concentration of sodium lauryl sulfate obtained from the titrimetric determination was 1.010 mg, and the SLS quantity was fixed as 1.0 mg per tablet for generic product development. The concentration of sodium in the given sample was found to be 2.16 µg/mL. Based on this value, the sodium concatenation in the reference tablet sample was calculated and found to be 0.54, and 0.08 mg of sodium is deducted from 0.54 mg due to 0.08 mg sodium being present in 1-mg of SLS. Thus, the sodium content from CCS alone was calculated and found to be 0.46 mg in the sample tablet, which is equivalent to 5.266 mg of croscarmellose sodium. The croscarmellose sodium quantity was fixed as 5.3 mg per tablet for generic product development. Quantification of binder was not carried out as the desired disintegration matching to reference product achieved with normal binder usage range of 1 to 2% and also with the aid of optimal concentration of disintegrant (CCS) based on quantification and ultimate dissolution profiling

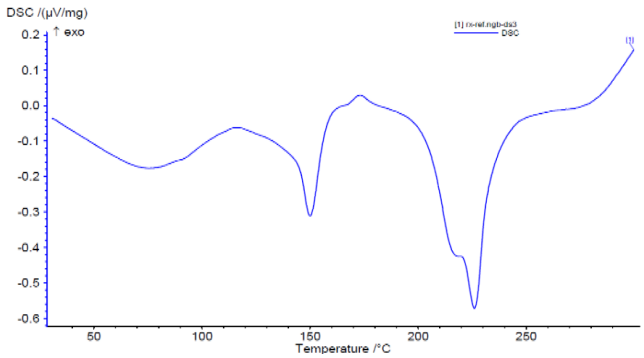

Figure 7: DSC thermogram of RLD

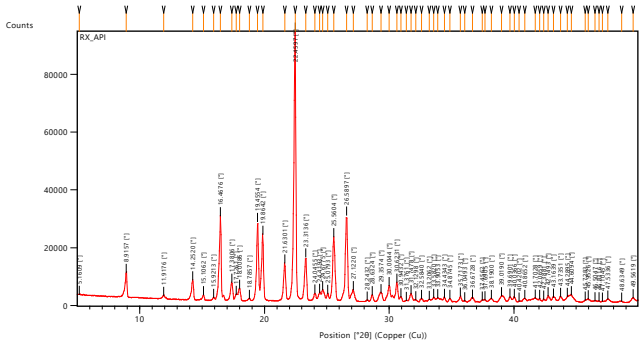

Figure 8: XRD diffractogram of rivaroxaban API (FORM-I)

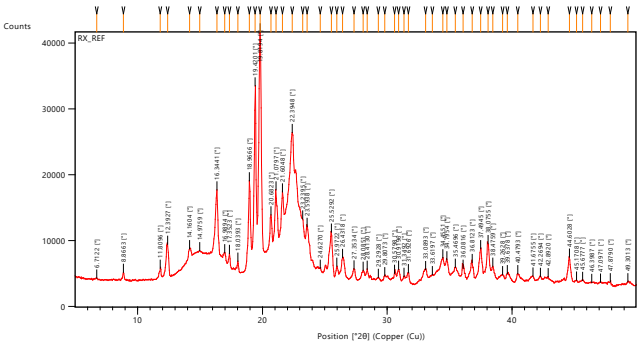

Figure 9: XRD diffractogram of RLD

Table 3: The final prototype formula derived after deformulation studies of the reference product

Component	*Function*	*Quantity (mg per tablet)*
Rivaroxaban(Rx)	Active	20.00
Lactose monohydrate (LCM)	Diluent	21.76
Microcrystalline cellulose (MCC)	diluent	38.64
HPMC)	Binder	1.80
Sodium lauryl sulphate	Solubilizer	1.00
Croscarmellose sodium (CCS)	Disintegrant	5.30
Magnesium stearate	Lubricant	1.50
Core tablet weight	--	90.00 mg
Coating material (Opdary)	Coating Material	2.00
Coated tablet weight	--	92.00 mg

matched to reference product. Quantification of HPMC was not carried out, but the HPMC quantity was fixed as 1.8 mg per tablet (2%) for generic product development based on usual binder range of 1 to 2%. The concentration of magnesium in the given sample was found to be 0.2440 µg/mL. Based on this value, the magnesium concatenation in the tablet sample was calculated and found to be 0.061 mg, which is equivalent to 1.5 mg of magnesium stearate. The magnesium stearate quantity was fixed as 1.0 mg per tablet for generic product development. The MCC quantity was fixed as 38.64 mg per tablet for generic product development. The final prototype formula derived after deformulation is presented in Table 3.

Identification of the Manufacturing Process

The granulation process adopted by the reference product was identified by visually observing the disintegration and disaggregation pattern during disintegration testing and by checking the nature of sediment in the dispersion showing granular appearance. Optical stereo-microscopic observation also showed the presence of granules (Figure 10). SEM images (Figure 11) showed presence of deformed granules in surface morphology from the crushed reference product tablets due to the compression force applied during tablet production.

In tactile evaluation, it was felt the presence of granular due to gritty particles but not very hard to break. Hence, it was expected to be the granules produced by using non-aqueous granulation.

Figure 10: Physical appearance of granules from crushed tablets observed under optical microscope.

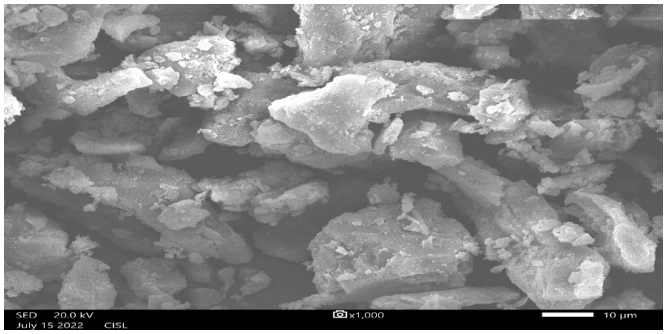

Figure 11: SEM photomicrograph - Surface morphology of crushed tablet of reference product

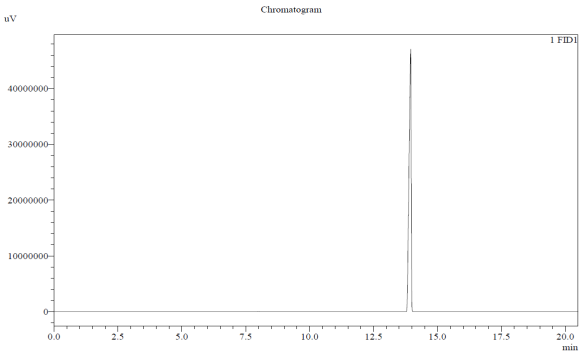

Figure 12: Ethanol content by HS-GC

Table 4: Identified CQAs from characterization of Xarelto® 20 mg film-coated tablets

S.N.	*Parameters*	*Results*
1.	Description	Round-shaped, biconvex film-coated tablets
2.	Ingredients	Core tablet Rivaroxaban Lactose monohydrate Microcrystalline cellulose Croscarmellose sodium Sodium lauryl sulphate Hypromellose, 2910 Magnesium stearate Coating Macrogol 3350 Hypromellose, 2910 Titanimum dioxide (E171) Iron oxide red (E172)
3.	Assay- 90.0–110.0%	99.9%
4.	NLT 80% (Q) of the labelled amount of Rivaroxaban dissolved in 30 mins	93%
5	Related Substance	
	Any unknown Impurity	0.02
	Total Impurities	0.06

Residual solvent content

A subsequent non-organic solvent content check revealed the presence of ethanol in reference product core tablets; hence, it was concluded that the reference was manufactured using a hydro-alcoholic or pure alcoholic granulation process (Figure 12). The actual aim here is not exactly to quantify the ethanol concentration but just to verify whether the manufacturing process utilized ethanol as a solvent. 1230 ppm of ethanol is found as residual ethanol left out after granulation. As a precaution, the tablet coat was removed during the analytical testing to avoid any interference due to the presence of alcohol in the film-coat.

Reverse engineering of innovator packaging material

The packaging components present in the reference product's packaging material was identified as aluminium-PVC-PVDC

by chemical testing and FTIR spectral matching of test samples of forming and lidding foils with standard spectrums from the FTIR spectral library. Physical dimensional measurements revealed the individual component's thickness and grammage. The complete study was described in our previously published work.[17] Hence, similar packaging components was considered for generic product.

Target CQA parameters for Generic product development derived from reference product

The final parameters generic product that was found with RLD can serve as a reference to match it as identical and comparable parameters by a pharmaceutically equivalent generic product to be developed are presented in Table 4. The impurity profile was carried out using the method described in USP.[18]

CONCLUSION

The current study decoded critical scientific information like API particle size, polymorphic form, and quantities of critical excipients present in Xarelto® 20 mg film-coated tablets. This information is a pre-requisite for the successful development of a robust, stable generic formulation of Rivaroxaban 20 mg film-coated tablets with the aim of achieving bio-equivalence with reference market product, Xarelto® 20 mg film-coated tablets. The reverse engineering methodology can play a very vital role in the development of generic products with a significant reduction in developmental cost, timelines, chances of failure of stability and in vivo performance.

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