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Decoding of API particle size in reference market product for bio-equivalent and cost effective generic product development

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ABSTRACT

Decoding or deformulation involves the characterization of the reference listed drug innovator drug where the most important step in deformulation is solid state characterization of API (Active pharmaceutical ingredient). Bioavailability and dissolution rate are directly impacted by API particle-size distribution. It aids in ensuring a bioequivalent formulation, particularly for medications with bioavailability that are dissolution-sensitive. Therefore, the information obtained from the innovator product's API's particle-size distribution is crucial for assuring solubility and bioequivalence. When a generic drug manufacturer experiences multiple Bioequivalence (BE) failures during the development of their product, it can lead to increased developmental costs and ultimately increased product cost the patients. The manufacturer may need to conduct additional studies and testing to optimize the formulation, which can be time-consuming and expensive. Therefore, it's critical to lower the chance of BE failures in order to lower the price of creating generic medicines and the financial burden on patients. Here conventional particle size determination methods are not useful, hot stage microscopy (HSM) is an ideal method , which can be beneficial with microscopic capturing of melting events in the melting point ranges of API and excipients components in a tablet dosage form. In this study, Xarelto 20 mg film-coated tablet was the reference product used and by using hot stage microscopy method, particle size distribution of reference API was found to be 77.4µ and Accordingly, the Rivaroxaban API particles are to be engineered for generic product design and development to have similar particle size distributions based on D90 and D50 values decoded from the reference market product. This can be useful to ensure similar drug performance and efficacy and ultimately favours the bioavailability and would be accessible to low cost as compare to the respective reference product.

Keywords: *Decoding, deformulation, reference listed drug, bioequivalence, generic product*

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INTRODUCTION

Generic product development usually begins with the characterization of the innovator product or Reference listed drug (RLD). Characterization of the RLD can involve anything from a thorough decoding of the quantitative formula to a simple identification of the release profile (for solid oral dosage forms) or pH and viscosity (for liquid orals) [1, 2]. By conducting a systematic and scientific review of the RLD, this crucial information can be acquired. This is also referred to as de-formulation studies. Deformulation analysis/Reverse Engineering is very useful in the pharmaceutical industry because it can help to ensure that products are safe, effective, and of high quality [3, 4]. Decoding of RLD begin with identifying the excipients and also identification of the excipients which affects the formulation's performance with respect to quality tests like stability and dissolution. These data will show the resources needed for reverse engineering in comparison to the value of the information obtained. The best candidates for reverse engineering are pH-adjusters, buffers, stabilisers (such antioxidants and chelating agents), and dissolution modifiers (like surface active agents) [3].

The most important step in deformulation is solid state characterization of API. Characteristics of API can be categorised as molecular, particle or bulk. Properties like crystalline forms, hydrates, solvates, and amorphous forms are all included at the molecular level [5, 6]. These forms differ in terms of solubility, manufactureability, bioavailability, and stability due to variations in intermolecular configurations and free energy. When developing generic products, these elements are crucial when describing the API solid form of the RLD[7, 8].

The most stable polymorphic form is typically used to create the innovator product to prevent transformation issues during processing and storage. To achieve a similar stability and dissolution profile, generics firms should utilise the same polymorphic form as the RLD [9].

Particle-size reduction or micronization is a common method used by pharmaceutical companies to improve the dissolution rate of poorly water-soluble drugs. Bioavailability and dissolution rate are directly impacted by API particle-size distribution. It aids in ensuring a bioequivalent formulation, particularly for medications with bioavailabilities that are dissolution-sensitive. Therefore, the information obtained from the innovator product's API's particle-size distribution is crucial for assuring solubility and bioequivalence. Hence this is challenge in determination of API particle size along with excipients. Due to their inability to distinguish between API and excipient particles, conventional particle-sizing methods based on light obscuration and laser scattering will not be useful. Microscopy is the only practical method can be used here [10].

On the basis of traits like particle shape and birefringence patterns, microscopy can distinguish APIs from excipients. Crystalline medications show birefringence patterns under polarised light, however many excipients are noncrystalline and don't show a birefringence pattern. Hot-stage microscopy can be supplemented with optical microscopy to confirm the API particles are identified according to their melting points. Hot stage microscopy is a technique used to study the behaviour of materials, including pharmaceuticals, under controlled heating and cooling conditions. To perform a hot stage microscopy study on an innovator product, a small sample of the product is placed on a glass slide, which is then inserted into a hot stage microscope [11, 12, 13]. The hot stage microscope is equipped with a heating element and a thermocouple, which allow the temperature to be controlled precisely. The sample is then heated and cooled at a controlled rate, while images of the sample are captured using a camera attached to the microscope. By analysing these images, the size and shape of the drug particles can be determined [14].

So, molecular and particle-level identification and characterization of the original drug's API speed up decision-making and cut down on development time. Therefore, identifying the particle size of the API in the innovator product is an important step in the generic product development process, as it can support faster and more successful development with reduced time, cost, and chances of failure [15].

When a generic drug manufacturer experiences multiple BE failures during the development of their product, it can lead to increased development costs. The manufacturer may need to conduct additional studies and testing to optimize the formulation, which can be time-

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consuming and expensive. Multiple BE failures can also result in approval delays and decreased profitability, which can raise the price of product development even higher. Therefore, it's critical to lower the chance of BE failures in order to lower the price of creating generic medicines and the financial burden on patients. The present study is about the characterization i.e. particle size determination of API with the help of hot stage microscopy study which aiming to replicate it as closely as possible and may help to increase the likelihood of bioequivalence and reduce the risk of BE failures [1, 3].

2. MATERIALS AND METHODS

2.1 Materials

Xarelto 20 mg film-coated tablet was procured from local pharmacy. Rivaroxaban API obtained as a gift sample from Mylan laboratories, India. Equipments and software used in this study were Hot stage microscope (Image provision LTX420 / BX53, India) and Software for image analysis was Image provision ipvPHot process, India.

2.2 Methods

2.2.1 Hot stage microscopy

The tablet of Xarelto 20 mg was crushed. Spread this sample uniformly over the microscopic glass slide. The glass slide was placed onto the hot stage attached to the upright microscope (Figure 1). Heating of sample ranged from room temperature to 250°C at a heating rate of 20-25°C/min. Then slower down the rate until completion of the study. , the hot- stage allows the temperature range from 0.1 up to 350 °C. The camera which is attached to the microscope was adjusted to focus the API particles. The morphological changes were observed and images of the samples were recorded at various temperatures during heating and cooling process. Comparison was done in between the particle size distribution of the API to that of the tablets to determine if the particle size is similar. . Analysis was carried out under 10X magnification. Thermal transitions were observed with the help of ipvPHot process imaging software and the particle size was measured at periodic intervals. The events were captured from onset to complete melting at different temperatures over the studied range, marked hot stage microscopic images were stored.

FIGURE 1: Hot stage microscope

2.2.2 Image analysis

Software ipvPHot (Figure 2) were used for image analysis. The images were stored across the melting zones but before that, complete melting were analysed for determination of particle size distribution of the Rivaroxaban API and Xarelto 20 mg film-coated tablets. The morphology of particles like size, shape, texture, intensity, solidity and circularity along with D10, D50, and D90 values were obtained through analysis carried out using ipvPHot process software.

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FIGURE 2: Software ipvPHot

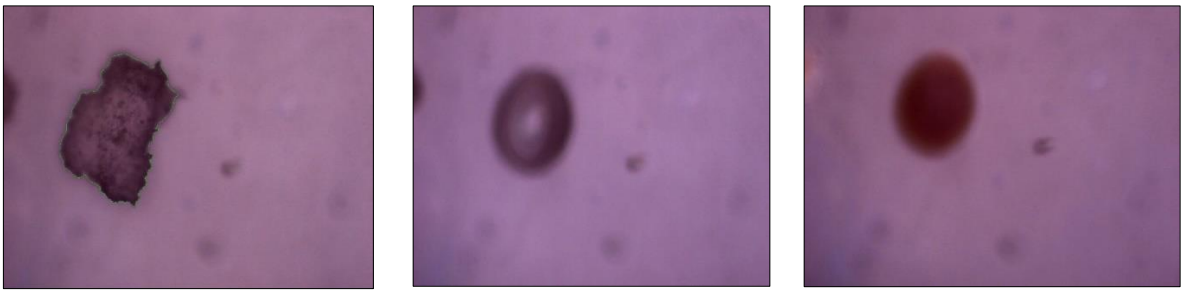
2.2.3 Particle size distribution

The particle size distribution of Rivaroxaban in the reference tablets was determined by plotting particle size vs. percent cumulative frequency.

3.RESULTS AND DISCUSSION

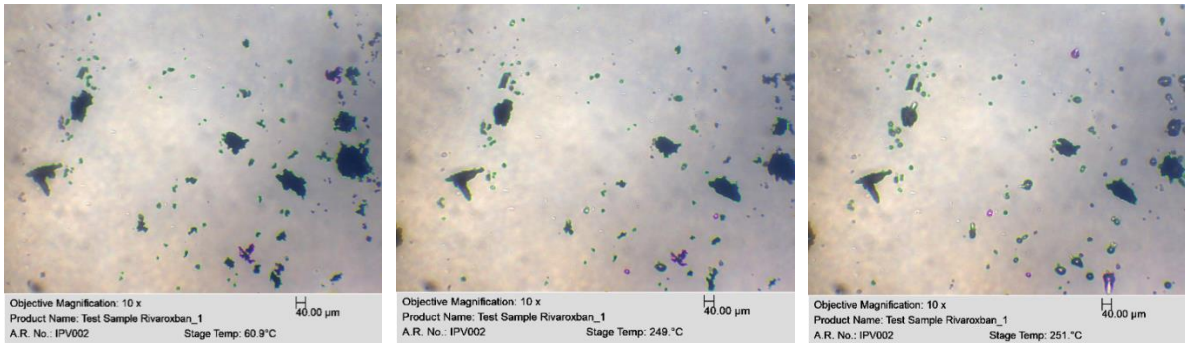
3.1 Hot stage microscopy

Rivaroxaban Particles were distinguished from excipients particles as they melted at different melting events during the heating cycle on HSM and with different morphological characteristics and pattern during melting events compared to Rivaroxaban API. The images for single point focused on particle has been shown in figure 3. And images of API melting at different temperature points has been shown figure 4.



(a) (b) (c)

FIGURE 3: (a) Rivaroxaban API particle observed during melting onset, (b) Rivaroxaban API particle during ongoing & continuous melting events, (c) Rivaroxaban API particle observed towards complete melting



Temp- 61.0°C Time- 0.0(sec) Temp- 249.°C Time- 480.0(sec) Temp- 251.°C Time- 540.0(sec)

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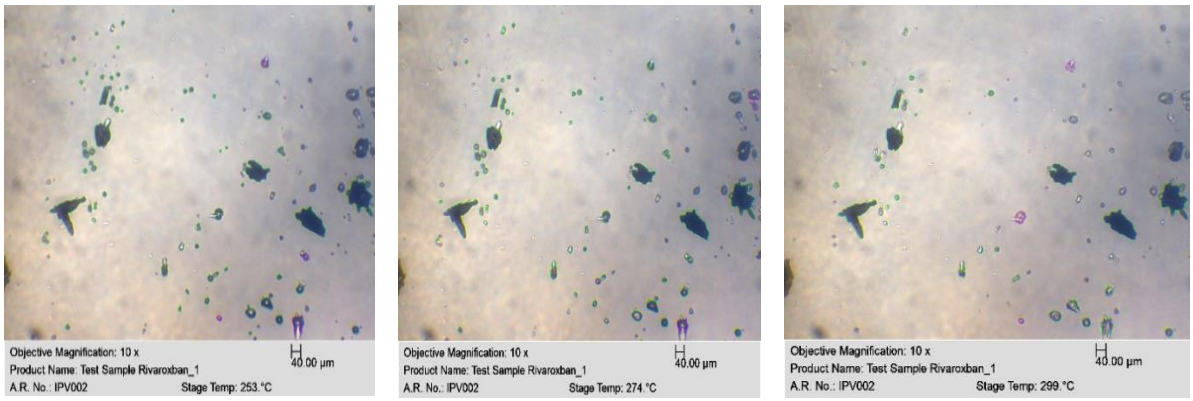

Temp- 253.°C Time- 600.0(sec) Temp- 274.°C Time- 960.0(sec) Temp- 299.°C Time- 1140.0 (sec)

FIGURE 4: Hot stage micro-photographic images captured at different temperature and time point

Melting points of the excipients in the reference tablets represented in table 1

TABLE 1: Melting points of excipients in reference tablets

Tablet Core Components	Melting Points
Inactive – Excipients	
1. Lactose Monohydrate	202.8 – 214 °C
2. Sodium Lauryl Sulfate	204 - 206 °C
3. Hypromellose (hydroxyl propyl methyl cellulose)	225-230 °C
4. Croscarmellose sodium	90°C
5. Microcrystalline cellulose	260-270ºC
6. Magnesium Stearate	359.4 °C

3.2 Image analysis

Particle size of about 77 particles were counted to evaluate the particle size distribution of the API. The morphology of particles like size, shape, texture, intensity, solidity and circularity along with D10, D50, and D90 values were obtained through analysis. These values and particle size is given in table 2

TABLE 2: Particle size of reference API

Parameter	Particles Size (µ)
D10	10.613
D50	25.739
D90	77.433

3.3 Particle size distribution

The PSD of Rivaroxaban in the reference tablets was determined by plotting particle size vs. percent cumulative frequency. The graph is shown in figure 5. Particle size of the API was found to be 77.4µ and average particle size D90 is shown in figure 6

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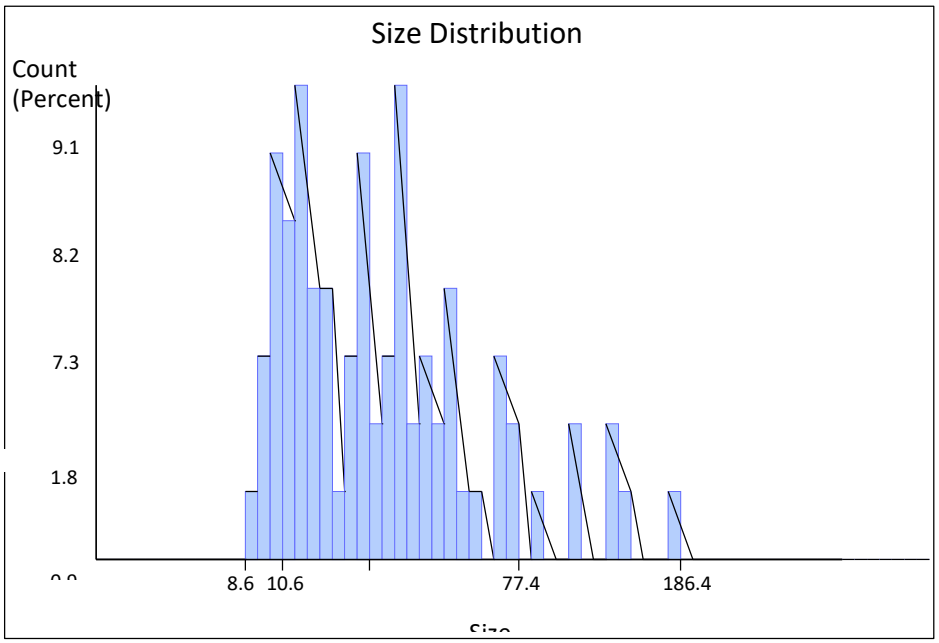

FIGURE 5: Particle size distribution of reference API

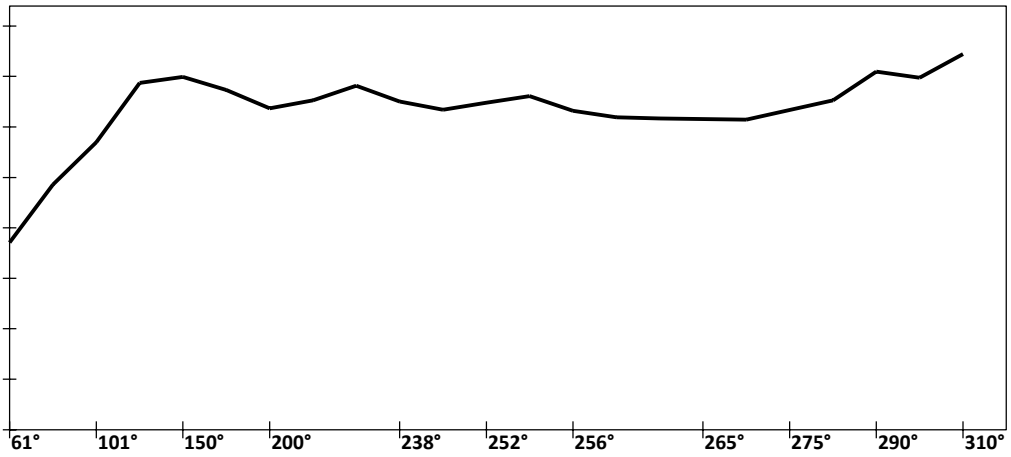

FIGURE 6: Average size D_{90}

Figure 7 and figure 8 represent the % circularity and texture of the API.

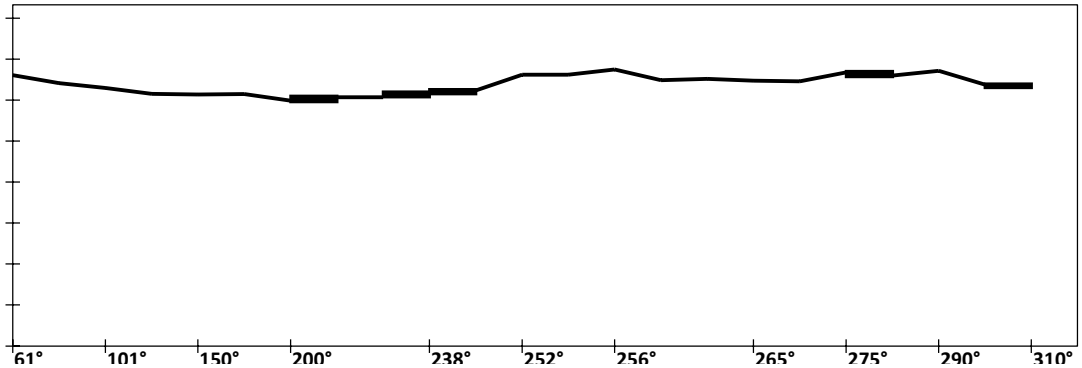

FIGURE 7: % circularity

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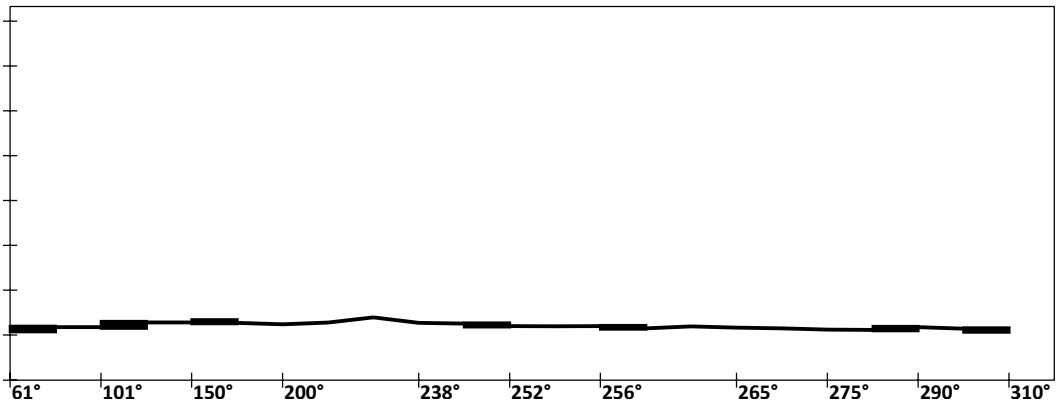

FIGURE 8: Texture of Rivaroxaban in the reference tablet

CONCLUSION

With the help of reverse engineering, the important and crucial parameter i.e. particle size distribution and particle size was determined which is very essential in achieving drug dissolution for poorly soluble drugs and bioavailability. The Hot stage microscopy was the technique used in this study thereby particle size was found to be 77.4µ and Accordingly, the Rivaroxaban API particles are to be engineered for generic product design and development to have similar particle size distributions based on mainly D90 value decoded from the reference market product. This can be useful to ensure similar drug performance and efficacy and ultimately favours the successful bioavailability and would be accessible to low cost as compare to the respective reference product.

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Author's contribution statement

All three authors have contributed in the experimental research design and in the analysis and interpretation of the results and to the writing of the manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none

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