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A Discriminatory Drug Dissolution Method for Estimation of Rivaroxaban from Rivaroxaban Tablets

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ABSTRACT

Purpose: *The objective of the present study is to develop discriminatory dissolution method to be used as a release parameter for testing and evaluating product performance by using quality by design trials intended for regulated markets.*

Methods: *The appropriate conditions were determined after testing solubility in dissolution medium, surfactant concentration, rotation speed, pH of the dissolution medium, apparatus type.*

Results: *Based on studies, the best dissolution conditions were achieved using a USP apparatus II, 900 ml of medium of 0.4% SLS in pH 4.5 acetate buffer at a rotation speed of 75 rpm.*

Conclusion: *This study demonstrates the systematic development of a discriminatory dissolution method for Rivaroxaban, a BCS Class 2 drug exhibiting pH-independent solubility. The dissolution method presented here can be used as a quality control test for Rivaroxaban tablet with special emphasis to understand in a batch to batch evaluation.*

Keywords: Sodium lauryl sulphate, Rivaroxaban; BCS class 2, Discriminatory.

INTRODUCTION

Oral dosage forms remain one of the most flexible and effective treatments available to patients. No matter which type of formulation, it undergoes sequential processes: (1) Disintegration or disaggregation i.e., release of the drug substance from the drug product; (2) dissolution, solubilization, or both, of the drug substance; and (3) absorption of the dissolved drug at the site of absorption. As all above tests are important for determination of bioavailability of drug, it is essential to have an appropriate *in vitro* dissolution method for prediction of *in vivo* performance [1].

Dissolution testing is a requirement for all solid oral dosage forms and is used throughout the development life-cycle for product release and stability testing. In general, dissolution testing is a prime requirement for all solid dosage forms and is used: 1) to guide development of new formulations; 2) to assure batch to batch variability; 3) to provide process control tool; 4) to check impact of particle size variation on dissolution; 5) impact of polymorphism on dissolution; 6) enabling the comparison of batches obtained from different production sources; 7) comparing new or generic formulations with an existing product; (8) assessing the stability of the drug product, helping in establishment of shelf life; 9) assessing product quality with respect to scale up and post approval changes; 10) as important tool for *in vitro-in vivo* correlation and 11) minimizing the need for bioequivalence studies [2]. It is a pivotal analytical test used for detecting physical changes in an active pharmaceutical ingredient and formulated product. At the early stages of the drug development process, *in-vitro* dissolution testing underpins the optimisation of drug-release from a given formulation. In particular, dissolution studies are quite predictive of *in-vivo* performance for insoluble or poorly soluble drugs (i.e., Biopharmaceutics Classification System (BCS) Class 2 drugs). Furthermore, a dissolution method with suitable discriminating power is preferred to indicate any possible changes in the quality of the product before *in-vivo* performance is affected. The discriminatory power of the dissolution method is the ability of the method to detect changes in drug product performance, generally demonstrated by determining the effect of deliberate changes in the formulation or process on dissolution characteristics [3].

Dissolution studies particularly are most important for insoluble or poorly soluble drugs, where absorption is rate limiting step. (i.e., Biopharmaceutics Classification System (BCS), class 2 drugs). Furthermore, development of discriminatory dissolution method is very challenging. The systematic development of a dissolution method of a discriminatory nature is required much earlier than at full-fledged product development. This enables the formulator to adopt the right approach in finalizing the prototype formula and process for further scale-up. In addition, demonstration of the discriminatory nature of the dissolution method to be used in routine quality control of commercial lots is expected by major regulatory agencies worldwide [4].

Rivaroxaban, with chemical name (5-Chloro-N-({(5S)-2-oxo-3-(4-(3-oxo-4-morpholinyl) phenyl)-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamideis) is an orally active, a Fxa inhibitor [5]. It is an anticoagulant that works by blocking certain clotting proteins in the blood. It prevents blood clots from forming due to a certain irregular heartbeat or after hip or knee replacement surgery. It is used to reduce the risk of stroke and blood clots in people with atrial fibrillation, not caused by a heart valve problem. Rivaroxaban drug is available in tablet strengths of 10, 15, and 20 mg. Rivaroxaban is slightly soluble in organic solvents (e.g. acetone) and is practically insoluble in water and aqueous media with pH 1-9 (pH-independent 5-7 mg/L-soluble at 25°C). The partition coefficient in octanol/water (log Po/w) is 1.5. It is a poorly soluble, highly permeable Biopharmaceutics Classification System (BCS) class II compound. As such, initial efforts are focused on developing a dissolution method that would be able to predict *in-vivo* performance.

MATERIALS AND METHODS

All the chemicals and solvents used for HPLC analysis were of analytical and HPLC grade respectively. The following chemicals were used to prepare buffers and HPLC mobile phase: orthophosphoric acid (AR grade), sodium acetate trihydrate (AR grade), sodium lauryl sulphate (AR grade), glacial acetic acid (AR grade), acetonitrile (HPLC grade), water (Milli-Q).

Instrumentation

Equipment and instruments used in the present study included: Balance (Mettler Toledo), tablet compression machine (Rimek mini press), dissolution test apparatus TDT-06T (Electrolab) and laboratory stirrer (Remi Instruments division) and HPLC (Dionex/Agilent).

Formulation preparation

Film-coated tablets of Rivaroxaban were prepared by two processes using the following excipients: calcium hydrogen phosphate anhydrous, croscarmelose sodium, magnesium stearate, microcrystalline cellulose, and opadry.

Solubility studies

Selection of dissolution medium may depend on solubility of drug. Saturation solubility at various pHs were determined by the shake-flask method. Solubility was performed in different aqueous medium (0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) with and without surfactant up to 24 hours. Samples were kept on shaker after ensuring the presence of excess solid in the sample in triplicates. The sample was stirred for 24 hours to achieve equilibrium, all samples were sampled and filtered through a 0.45 µm nylon filter, and the concentration of rivaroxaban was determined by a validated HPLC method.

Dissolution studies

The dissolution method was developed using a TDT-06T dissolution apparatus. Volume of dissolution medium i.e., 900 ml was selected based on the solubility data. Influences of rotation speed and surfactant concentration in pH 4.5 Acetate buffer were evaluated. At 5, 10, 15, 30, 45, 60 minutes time interval, 10 ml sample aliquots were withdrawn and replaced with an equal volume of fresh medium to maintain a constant total volume. Aliquots were passed through a filter and analyzed using the previously validated HPLC method.

Sample analysis

Sample analysis was performed using UV-Vis detector. The validated reversed-phase HPLC method employed a 250 mm × 4.6 mm, 5 µm: (Zorbax SB CN is suitable or equivalent) maintained at 35°C with a mobile phase composed of buffer (1 ml orthophosphoric acid in 100 ml water): acetonitrile (50:50, v/v) at a flow rate of 1.2 ml/min with detection at 240 nm.

RESULTS AND DISCUSSION

Solubility study

As rivaroxaban is having poor solubility, achievement of sink condition is a big task. From solubility study it was observed that it has pH independent solubility as summarized in Table 1. Solubility data is having influence on sink condition.

To provide sink condition surfactant evaluation was done. Increase in solubility was found when surfactants were added in aqueous medium. Selection of surfactant was based on critical micelle concentration (CMC) of each of surfactant. Maximum effect on solubility was found by SLS (Sodium lauryl sulphate) indicating minimum amount required to bring sink condition in limited volume of dissolution media. Also being most popular surfactant suggested by FDA to use in dissolution media, SLS was selected as suitable surfactant for dissolution method development.

Various concentration of SLS (Sodium lauryl sulphate) were optimized in physiological buffers. In 0.1 N HCl with 0.25% SLS, 0.032 mg/ml solubility of rivaroxaban was observed whereas in pH 4.5 acetate buffer with 0.25% SLS and in pH 6.8 phosphate buffer with 0.25% SLS solubility showed similar results i.e., 0.05 mg/ml (Table 2).

Dissolution medium selection

Media that follow more closely the composition of fluids in the stomach and intestinal tract is selected as dissolution medium. The composition of the dissolution medium was selected on the basis of solubility data at 37°C. Solubility data revealed that addition of surfactant may be suitable as a dissolution medium. The suitability of dissolution medium (0.4% sodium lauryl sulphate in pH 4.5 acetate buffer) relative to the other dissolution medium was evaluated. Upon comparing solubility data along with different concentration of SLS it was observed that 0.1 N HCl with 0.4% SLS does not achieve sink condition. Hence, pH 4.5 Acetate buffer was selected as dissolution medium as it shows sink condition for 20 mg strength. pH 4.5 Acetate buffer with 0.2% SLS was selected as dissolution medium for 10 mg strength. Regulatory agencies accept discriminatory dissolution methods for the quality control of the pharmaceutical products, especially oral solid dosage forms.

To be a proper dissolution method it should have 1) low variability (% RSD less than 20% at initial timepoint and less than 10% for later time point, 2) understanding of dissolution results, 3) discrimination between batches and 4) reproducible.

Medium	**Solubility in mg/ml***
0.1N HCl	0.005
pH 4.5 Acetate buffer	0.007
pH 6.8 phosphate buffer	0.006
Water	0.006
*n=3	

Table 1: Solubility of rivaroxaban in aqueous medium without SLS in mg/ml.

Media	**0.1% SLS**	**0.2% SLS**	**0.25% SLS**	**0.3% SLS**	**0.4% SLS**	**0.5% SLS**	**0.75% SLS**	**1.0% SLS**
	n=3							
0.1 N HCl	-	-	0.032	-	-	0.059	0.085	0.112
pH 4.5 acetate	0.023	0.043	0.047	0.064	0.084	0.103	0.158	0.175
buffer								
pH 6.8 phosphate	-	-	0.049	-	-	0.083	0.135	0.174
buffer								
Water	-	-	0.032	-	-	0.095	0.148	0.21

Table 2: Solubility data comparison of different concentration of SLS in physiological buffers in mg/ml.

Dissolution method

Based on above points, dissolution study was performed with and without SLS, at different RPM and on different concentration of SLS.

Firstly to support solubility data and to check impact of excipient on solubility of drug, dissolution was performed at 75 rpm, 900 ml in pH 4.5 acetate buffer without surfactant. At the same time dissolution with 0.4% SLS was also performed (Figure 1). The data clearly indicates the drug shows only 45% of release in pH 4.5 acetate buffer. To demonstrate effect of rpm dissolution was carried out with 0.4% SLS in pH 4.5 acetate buffer. 50 rpm and 75 rpm data was generated and observed; 50 rpm shows more variability in results as compared to 75 rpm. Hence, 75 rpm was selected for dissolution method (Figure 2).

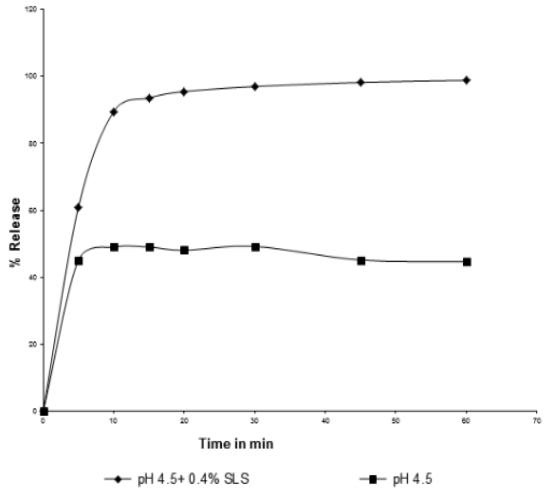

Figure 1: Dissolution data generated on same batch with and without SLS at 75.

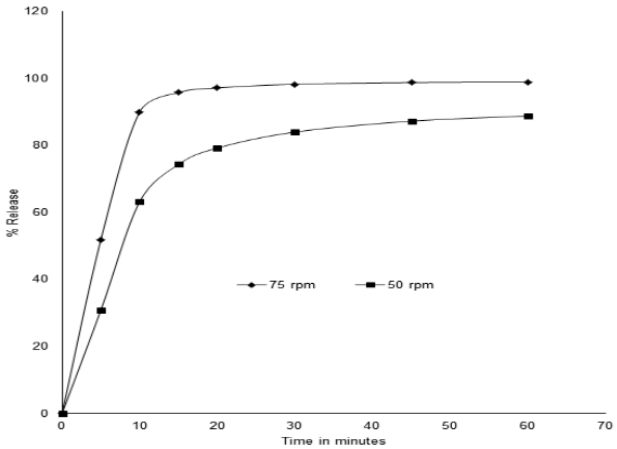

Figure 2: Dissolution data generated on same batch with different RPM in pH 4.5 acetate buffer with 0.4% SLS.

Based on solubility data and to confirm sink condition dissolution was performed at different concentration of SLS at 75 rpm, 900 ml, apparatus II paddle. It was observed that in 0.1% SLS, 60-75% release was observed when dissolution was ran up to 60 minutes. More than 85% of drug release was observed in 15 minutes for 0.2%, 0.3% and 0.4%. But again variability was more in 0.2% SLS. 0.3% shows no variability but as sink condition was not achieved so 0.4% SLS was selected as surfactant concentration (Figure 3). To prove discriminatory nature of dissolution formulation trials was taken as per quality by design and the optimized method showed discrimination at 75 rpm, 900 ml dissolution volume in pH 4.5 acetate buffer with 0.4% SLS.

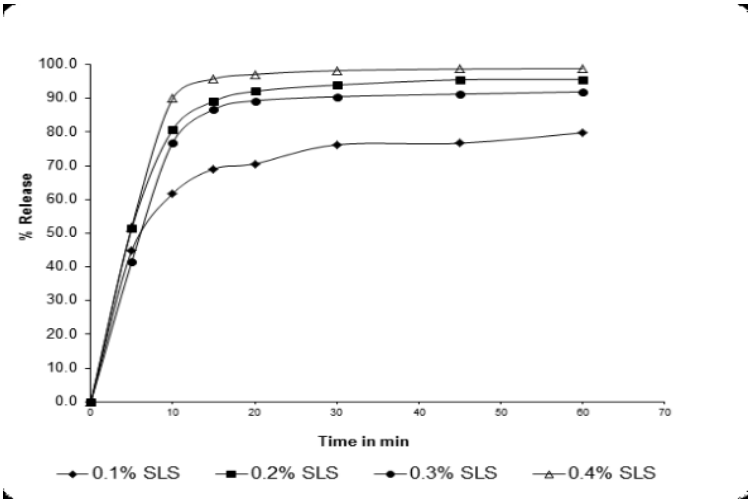

Figure 3: Dissolution data generated on same batch with different concentration of SLS in pH 4.5 acetate buffer.

CONCLUSION

This study demonstrates the systematic development of a discriminatory dissolution method for rivaroxaban, a BCS Class 2 drug exhibiting pH-independent solubility. The dissolution method presented here can be used as a quality control test for Rivaroxaban tablet with special emphasis to understand in a batch to batch evaluation. In the present study, an attempt has been made to develop discrimination dissolution medium for Rivaroxaban tablets. Which provide the discriminatory results when different pH condition, RPM and apparatus.

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CONFLICT OF INTEREST

Nil.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with animal and human subjects performed by the author.

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