Development and Validation of a Selective Online Dissolution Method for Rosiglitazone Maleate

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Abstract

A new specific, accurate, precise, and reproducible selective online dissolution method for rosiglitazone maleate is developed and validated for the dissolution of rosiglitazone maleate in pharmaceutical formulations. The rationale of the method is based on the direct measurement of the absorbance of the analyte in the buffer medium at 242 nm using buffer as blank. Dissolution is achieved on a dissolution test apparatus consisting of photo diode array spectrophotometer, peristaltic pump, and temperature controller, using 0.01N HCl and 0.05M potassium chloride as the dissolution medium. The proposed method is developed, optimized, and validated in terms of linearity, reproducibility, accuracy, and selectivity for the dissolution of rosiglitazone maleate in pharmaceutical formulations. The method is found to be linear in the range of 1 to 14 µg/mL of rosiglitazone maleate with a correlation coefficient of 0.999. The dissolution studies of rosiglitazone maleate tablets obtained by the proposed method are in good agreement with those by high-performance liquid chromatography.

Introduction

Rosiglitazone is a drug that reduces the amount of glucose (sugar) in the blood. It is in the class of anti-diabetic drugs called "thiazolidinediones" that are used for the treatment of type II diabetes (1,2). Preclinical studies have shown that rosiglitazone maleate is a highly selective and potent agonist for the peroxisome proliferators-activated receptor-gamma. Apart from its effect on insulin resistance (3), it appears to have an anti-inflammatory effect (4).

Chemically, it is known as 5-{[4-(2-methyl-2-pyridinylamino) ethoxy] phenyl} methyl-2, 4-thiazolidinedione (Figure 1). Rosiglitazone often is referred to as an "insulin sensitizer" because it attaches to the insulin receptors on cells throughout the body and causes the cells to become more sensitive (more responsive) to insulin. As a result, more glucose is removed from the blood. Few methods have been reported on the quantitative determination of rosiglitazone maleate by high-performance liquid chromatography (HPLC) (4–7). However no methods have been reported for dissolution studies. Rosiglitazone maleate is insoluble or sparingly soluble in water, and it is not official in any of the pharmacopoeia. Dissolution characteristics of insoluble or sparingly soluble drugs have always been a challenge to the pharmaceutical industries (5,8); therefore there is ample scope for the development of newer selective online dissolution methods.

The present study was aimed at developing online dissolution for routine and selective analysis of rosiglitazone maleate in commercially available and in-house prepared pharmaceutical formulations. The mixture of 0.01N hydrochloric acid and 0.05M potassium chloride was used as the dissolution medium for the estimation of the drug from the formulation in order to obtain the dissolution profile. Dissolution was achieved on an online photo diode array spectrophotometer, peristaltic pump, and temperature controller (VK 750D). The proposed method was developed, optimized, and validated in terms of linearity, reproducibility, accuracy, and selectivity for the dissolution of rosiglitazone maleate in pharmaceutical formulations.

Experimental

Material and apparatus

Rosiglitazone maleate was obtained from Biocon (Bangalore, India). All the other reagents were of reagent grade, and the solvents of HPLC grade. Acetonitrile, orthophosphoric acid (85%), potassium chloride, hydrochloric acid, ammonium

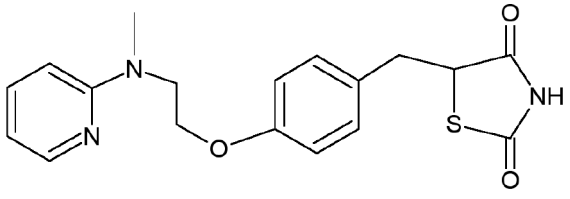

Figure 1. Chemical structure of rosiglitazone maleate.

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dihydrogen orthophosphate, and potassium dihydrogen phosphate were purchased from Panreac (Barcelona, Spain) and triethylamine from Acros (Geel, Belgium).

HPLC-grade water was prepared using a Millipore water system and used for the preparation of the mobile phase. The mobile phase was filtered through 0.45-µm filters (Millipore, Billerica, MA) after preparation. Purified water was used for the preparation of the dissolution medium. The excipients lactose, microcrystalline cellulose, sodium starch glycolate, povidone k-30, magnesium stearate, colloidal silicon dioxide, and coating material opadry, propylene glycol, and dimethicon were imported from various parts of the world. Tablet formulations containing rosiglitazone maleate (Avandia 4 and 8 mg) were purchased from the local market, manufactured by Smithkline Beecham Corporation (Philadelphia, PA), and in-house rosiglitazone maleate (4 and 8 mg) was formulated in our research and development laboratory. Vankel dissolution test apparatus consisting of a model VK7000 attached to an Agilent model 8453 photo diode array spectrophotometer (Agilent, Palo Alto, CA). A peristaltic pump and temperature Model-VK 750D were used for online dissolution. The samples collected from the dissolution vessel after 45 min were filtered through a 0.45-µm filter and analyzed on a HPLC instrument consisting of a Shimadzu (Koyoto, Japan) model LC-2010A_{HT} automatic liquid chromatograph system, with built in UV–vis detector and autosampler and with a PC integrator was used. The chromatograms were analyzed using ClassVp software provided along with the system.

Chromatographic conditions

The samples collected from the dissolution vessel after 45 min were analyzed on an Inertsil ODS-III column (250 × 4.6-mm, 5 µm) under isocratic conditions. The flow rate was adjusted to 1 mL/min, the sensitivity was 0.0001AUFS, and the wavelength of the UV detector was set to 242 nm. Injection volume was 10 µL. The mobile phase consisted of a mixture of acetonitrile and buffer in the ratio of 50:50 (v/v). The buffer solution was prepared by mixing 3.45 g ammonium dihydrogen phosphate, 4.08 g potassium dihydrogen orthophosphate, and 3 mL triethylamine in 3 L of HPLC-grade water. The pH of the buffer solution used was adjusted to 5.0 with orthophosphoric acid. All experiments were conducted at 25°C. The mobile phase was run through the column for at least 1 h before analysis in order to stabilize the HPLC system.

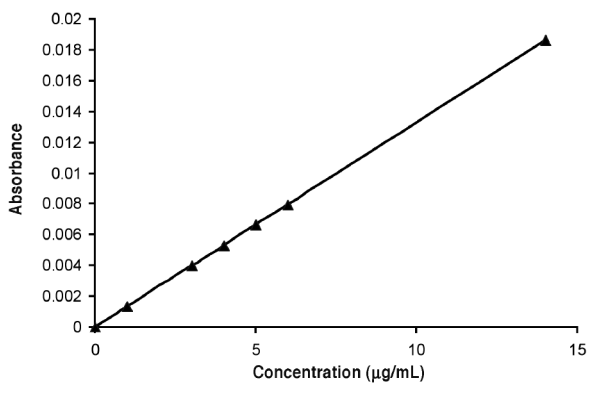

Figure 2. Calibration curve of rosiglitazone maleate with five different concentrations in the dissolution medium consisting of a mixture of 0.01N hydrochloric acid and 0.05M potassium chloride.

Dissolution conditions

The dissolution medium consisted of a mixture of 0.01N hydrochloric acid and 0.05M potassium chloride. Before use, the dissolution medium was mixed thoroughly and degassed by sonication. A 900-mL volume of dissolution medium was used for dissolution. The dissolution apparatus was set at 100 rpm, and its temperature was maintained at 37°C ± 0.5. USP apparatus II (paddle) was used for dissolution. The photo diode array spectrophotometer (Agilent) was set at 242 nm, and the online sampling point was set at time 0, 5, 10, 15, 20, 25, 30, 35, 40, and 45 min in the Chemstation software (Agilent). Before starting the dissolution, blank and medium tests were performed using the proposed dissolution medium. The dissolution system was stabilized for at least 30 min at 37°C ± 0.5 before analysis.

Optimization of dissolution medium

Different compositions of the dissolution medium were investigated: 0.01N and 0.1N hydrochloric acid, acid phthalate buffer pH 2.8, 3.8, and 4.0, neutralized phthalate buffer pH 4.4, 5.2, and 5.8, acetate buffer pH 4.5, 5.1, and 5.5, in 500 and 900 mL volume. For the selection of the dissolution medium, the criteria was the release profile of the rosiglitazone maleate, ease of sample preparation, and applicability of the method for online dissolution purposes.

Construction of calibration curve

Primary stock solution of 0.2 mg/mL of rosiglitazone maleate was prepared in methanol. Different aliquots of this primary stock solution were transferred to a series of 50-, 100-, and 200-mL standard volumetric flasks, and the volume was made up with methanol. Five different concentrations of rosiglitazone maleate (1, 3, 4, 5, 6, and 14 µg/mL) were prepared in the dissolution medium for the calibration curve in order to cover the three strengths of rosiglitazone maleate tablets (2, 4, and 8 mg). To establish the linearity of the proposed method, the concentration was plotted against the absorbance of the analyte (Figure 2). Least square regression analysis was carried out for the obtained data.

Validation of the method

To study the selectivity of the method, a placebo mixture of approximately 400 mg was added into the dissolution vessel containing 900 mL of the dissolution medium. The resulting solution was analyzed online at 242 nm. The common excipients lactose, microcrystalline cellulose, sodium starch glycolate, povidone k-30, magnesium stearate, colloidal silicon dioxide, coating material opadry, propylene glycol, and dimethicon were analyzed online separately and checked for interference near the selected wavelength at 242 nm.

Accuracy of the proposed method was determined at three

different levels of drug concentrations for rosiglitazone maleate: 1st level, 2 µg/mL; 2nd level, 9 µg/mL; and 3rd level, 14 µg/mL. These were prepared independently from the stock solution and analyzed online (n = 6). The accuracy was assessed as the percentage relative error and mean percentage recovery. Different concentrations of the pure drug rosiglitazone maleate (2, 9, and 14 µg/mL) were added to a known pre-analyzed formulation sample and analyzed using the proposed method (n = 5) to check accuracy (Table I). The percent recovery of the added pure drug was calculated as, % recovery = Cv – Cu/Ca × 100, where Cv is the total drug concentration measured after standard addition; Cu is drug concentration in the formulation, and Ca is the drug concentration added to the formulation. Repeatability was determined by using different levels of drug concentrations (as mentioned previously for accuracy), prepared from the stock solution and analyzed (n = 6).

Table I. Accuracy and Precision Data of the Developed Method. Each Determination is the Result of Five Separate Determinations

Level	Concentration (µg/mL) Drug added	Amount of drug found mean (± SD)	% RSD	Mean % recovery (± SD)
1st	2	1.9996 ± 0.0214	1.072	99.98 ± 1.081
2nd	9	9.0201 ± 0.0562	0.623	100.22 ± 0.628
3rd	14	13.999 ± 0.0791	0.565	99.99 ± 0.567

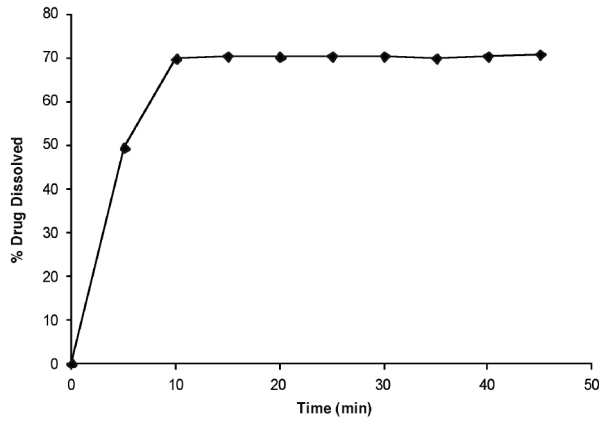

Figure 3. Dissolution profile of maximum drug release in 0.01N hydrochloric acid.

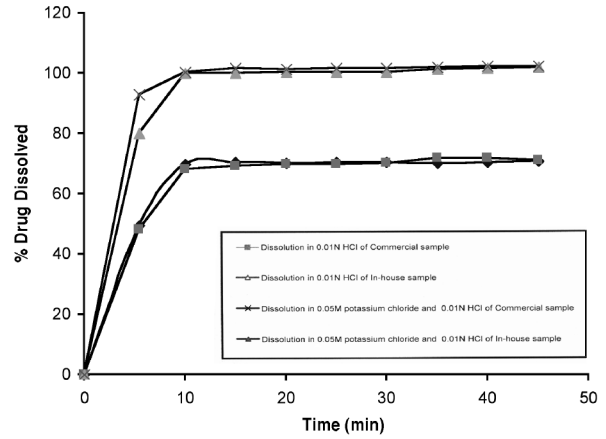

Figure 4. Addition of 0.05M potassium chloride to 0.01N hydrochloric acid increased drug release to 100%.

Estimation from formulations

The dissolution apparatus was set at 100 rpm with USP apparatus II (paddle). The dissolution vessels containing 900 mL of the dissolution medium were equilibrated at 37°C ± 0.5. Before running the system blank and medium tests were performed on the dissolution apparatus. Six tablets were weighed individually (Avandia 4 or 8 mg and in-house prepared rosiglitazone maleate film coated tablets containing 4 or 8 mg rosiglitazone) and transferred to each of the six dissolution vessels containing the dissolution medium. Online absorbance was recorded at intervals of 0, 5, 10, 15, 20, 25, 30, 40, and 45 min. Calculations were made directly through the software. The same samples were collected from the dissolution vessels after 45 min, filtered through 0.45-µm membrane filter paper, and the samples were analyzed using HPLC in order to ascertain the accuracy of the method.

Results and Discussion

In the dissolution medium containing 0.01N and 0.1N hydrochloric acid, acid phthalate buffer (pH 2.8, 3.8, and 4.0), neutralized phthalate buffer (pH 4.4, 5.2, and 5.8), and acetate buffer (pH 4.5, 5.1, and 5.5), the maximum drug release was found to be approximately 60–70% (Figure 3). The other dissolution profile is not shown. Addition of 0.05M potassium chloride to 0.01N hydrochloric acid in the dissolution medium increased the drug release to 100% within 10 min in the commercial as well as in-house prepared formulations (Figure 4).

Table II. Comparative Online and HPLC Dissolution Data of Rosiglitazone Maleate in Dosage Forms (Each Value is for Individual Tablets)

Sample No.	Online Dissolution (%)	HPLC Dissolution (%)
1	101.20	100.55
2	101.33	102.44
3	100.15	101.22
4	99.99	100.25
5	100.56	101.00
6	102.23	101.75

Table III. Application of the Developed Online Dissolution Method to the Determination of Rosiglitazone Maleate in Dosage Forms (Each Value is the Average of Six Tablets)

Commercial product	% Dissolution	Mean ± SD	% RSD
Avandia 4 mg tablets	98.99	± 0.981	0.991
Avandia 8 mg tablets	99.99	± 1.021	1.022
Rosiglitazone 4 mg tablets*	101.1	± 0.819	0.810
Rosiglitazone 8 mg tablets*	102.1	± 0.790	0.773

* Formulation was prepared in the research and development lab.

Based on these experiments, optimum drug release was obtained with a dissolution medium consisting of a buffer of 0.01N hydrochloric acid and 0.05M potassium chloride.

In the selected dissolution medium, the linear range was found to be 1–14 µg/mL. Linear regression analysis, the slope (± standard error) and intercept (± standard error) were found to be 102.2 (± 0.108.5) and –436 (± 106.4), respectively. These mean values were found to be within 95% confidence limits (confidence limits of the slope 102.2 to 102.8: confidence limits of the intercepts –810.5 to –658.2). Goodness of fit of the regression equation was supported by the high regression coefficient value 0.999. Lower values like standard error slope intercept and estimate the indicated high precision of the proposed method.

The blank samples containing excipients did not show any interference near the drug absorbance. Similar results were observed with all the other individual excipients. In the presence of the excipients, peak absorbance was not affected.

The proposed dissolution medium containing the buffer mixture (0.01N hydrochloric acid and 0.05M potassium chloride) showed 100% drug release within 10 min (Figure 4). Accuracy of the proposed method was determined at three different levels of drug concentrations for rosiglitazone maleate (1st level, 2 µg/mL; 2nd level, 9 µg/mL; and 3rd level, 14 µg/mL). All three concentration levels showed an accuracy nearly 100%, mean % recovery values and their low standard deviation values of 1.072 represented the accuracy of the method. The samples collected from the dissolution vessels after 45 min were analyzed by HPLC. The dissolution results obtained by HPLC were comparable and accurate with respect to online results (Table II). These results supported the applicability of this method to an online dissolution. The proposed method was evaluated by the dissolution of rosiglitazone maleate in pharmaceutical formulation. The dissolution values of rosiglitazone maleate for a commercially available formulation and in-house formulation were found to be very close to the label claim (Table III). These results supported the applicability of this method to the solid dosage forms.

Conclusion

The recoveries in formulations were in good agreement with their respective label claims, indicating non-interference of the excipients in the dissolution determination of the drug. Validation parameters of the proposed online dissolution method prove high selectivity, accuracy, and precision. The proposed method is simple and rapid, and hence can be utilized for the routine quality control analysis of rosiglitazone maleate in pharmaceutical formulations.

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