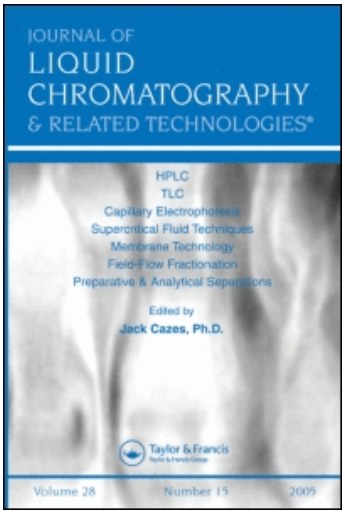

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Abstract: A rapid and validated RP-HPLC method with UV detection has been developed to determine rosiglitazone maleate in raw material, pharmaceuticals, and in-vitro drug dissolution studies. The analysis was carried out using a reversed phase C_8 column (250 mm × 4.6 mm) and a mobile phase composed of acetonitrile: methanol: acetate buffer (30:20:50 v/v/v). The method was validated according to the ICH guidelines. The method produced linear response over the range of 5–100 $\mu g\,mL^{-1}$. The method was successfully applied for the determination of the drug in tablet dosage form, polymeric microspheres, and in-vitro drug dissolution. No interference was observed from the excipients of tablets, microspheres, and drug dissolution studies.

Keywords: Dissolution, Kinetic model, Polymeric microspheres, Rosiglitazone maleate, RP-HPLC, Validation

INTRODUCTION

Rosiglitazone maleate (RGM), (±)-5-[{4-[2-(methyl-2pyridinyl amino) ethoxy] phenyl} methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate (Fig. 1),

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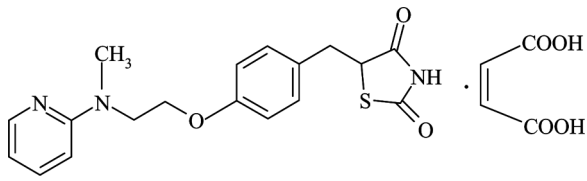

Figure 1. Structure of rosiglitazone maleate.

is a new class of oral anti-diabetic drugs used in the treatment of type-II diabetes (NIDDM) and belongs to the thiazolidinedione family. It is a potent peroxisome proliferator activated gamma receptor (PPAR-γ) agonist, which improves glycemic control by improving insulin sensitivity while reducing circulating insulin levels. Peak serum levels are achieved about 1 hour after oral administration of 2 mg conventional tablet of RGM, bioavailability approaches 99%. It is approximately 99.8% protein bound, and it has an elimination half-life of 3–4 h.

The drug is not yet official in any pharmacopoeia. Several methods have been reported in the literature for the determination of RGM in pharmaceuticals and human plasma. He et al. reported a sophisticated method based on HPLC with mass spectrometry.[1] Muxlow et al.,[2] Mamidi et al.,[3] Hruska et al.,[4] Mamidi et al.,[5] Kim et al.,[6] Pedersen et al.,[7] and Kang et al.[8] all describe HPLC methods using flouresecense detection. Gomes at al.[9] reported the only HPLC method using UV detection at 247 nm. The method was applied for determination of RGM in coated tablets. Most of these reported methods require solid phase extraction or expensive equipment, which are not economically acceptable for routine use in pharmacokinetic and pharmaceutical studies that require analysis of larger number of samples regularly. Due to the widespread use of HPLC in routine analysis, it is important to develop HPLC methods, which are reliable, sensitive, and thoroughly validated.

RGM is practically insoluble in water. When a poor water soluble drug is administered orally its dissolution may be the rate limiting step during its absorption from g.i.t and, hence, its onset of action is delayed. Therefore, drug dissolution testing is an integral part of pharmaceutical product development and routine quality control monitoring of drug release characteristics. Moreover, this dissolution testing is considered to be a sensitive, reliable, and rational tool for predicting in-vivo drug bioavailability behavior.[10–13] To the best of our knowledge, drug dissolution studies and determination of this drug from polymeric microspheres have not yet been reported in any scientific literature.

The aim of the present investigation is to develop a rapid, accurate, and validated RP-HPLC method with UV detection for quantification

of RGM from polymeric microspheres and in-vitro dissolution studies for quality control purposes. In the present study, we have developed a validated HPLC method using UV detection with low retention time, over existing HPLC procedures suitable for analysis of a larger number of samples.

EXPERIMENTAL

Chemicals and Reagents

The HPLC grade acetonitrile, ammonium acetate, and acetic acid were purchased from Merck (India). High performance liquid chromatographic grade water was prepared by reverse osmosis and further purified by passing through a Milli Q system (Millipore company, Milford, MA). RGM was provided by M/S Torrent Pharmaceuticals Ltd. (Ahmedabad, India) as gift sample. Rezult®4 (Sun Pharmaceuticals, Jammu, India) tablets containing RGM were procured from a local pharmacy. A stock solution of RGM (100 μg/mL) was prepared in methanol. This stock solution was further diluted to produce the concentrations in the range of 0.25 μg/mL to 100 μg/mL. The stock solutions were stored in the dark at 4°C. No instability was observed from the solution stored under these condition compared to fresh daily diluted ones, since there was no change in the peak height of RGM or no appearance of any impurities.

Preparation of RGM Microspheres

Microspheres containing RGM were prepared by the emulsion solvent evaporation technique according to Bogataj et al.[14] Ammonio methacrylate copolymer (Eudragit® RS100) was used as coating polymer. The formulation was comprised of 33.33% RGM and 66.67% polymer. Briefly, the required amount of polymer was dissolved in acetone. An appropriate quantity of RGM was added to the polymeric solution to prepare a smooth suspension. Later, the suspension was poured into 40 mL of HLP kept at 30° ± 1°C, while stirring at 800 rpm by a PMDC stirrer (RQ-121/D, Remi, India). After evaporation microspheres formed were colleted by filtration and washed 3 times with petroleum ether and dried under vacuum at room temperature overnight.

Instruments and Chromatographic Conditions

HPLC analyses were performed using a Jasco Chromatographic System (JASCO, Japan) equipped with a Jasco-PU-980 pump and a Jasco-UV-975

UV detector. Data analyses were carried out using Clarity Lite® software. The separation was carried out at ambient temperature, on a reversed phase Fine Pak SIL C_8 steel column (250 mm × 4.6 mm, Jasco, Japan). The chromatographic separation was performed in isocratic mode.

The dissolution studies from the pharmaceutical formulations were performed on a paddle type 6-station dissolution test apparatus (TDT-06P, Electrolab, India).

The mobile phase was acetonitrile: methanol: acetate buffer with pH 4.0 (30:20:50 v/v/v) and delivered at a flow rate of 1.5 mL min^{-1}. The injection volume was 20 μL. The elute was analyzed at a wavelength of 260 nm.

Preparation of Standard Solution of Rosiglitazone Maleate

A stock standard solution of 100 μg/mL were prepared by dissolving 10 mg of RGM reference standard in a sufficient quantity of methanol in a 100 mL volumetric flask, and stirred in an ultrasonic bath for 10 minutes. The volume was adjusted with methanol.

Sample Preparation for Analysis of Tablets and Determination of Encapsulation Efficiency of Rosiglitazone Maleate Microspheres

Microspheres containing RGM equivalent to 10 mg of the drug based on theoretical drug content were crushed in a glass mortar. The content was carefully transferred to a 100 mL volumetric flask with 50 mL of acetate buffer (pH 4.0). The glass mortar was washed with the same buffer and added to the volumetric flask to make up the volume 100 mL. The acetate buffer containing crushed microsphere was stirred in a thermostatically controlled water bath for 45 min in order to extract the drug efficiently in acetate buffer. Then it was filtered through 0.22 μm membrane filter. A 5 mL volume of this solution was diluted with mobile phase in a 50 mL volumetric flask to obtain a concentration of 10 μg/mL.

For sample preparation from the tablets, twenty tablets (Rezult® 4) containing label claimed 4 mg RGM were finely powdered. An accurately weighed portion equivalent to 10 mg of the drug was quantitatively transferred to a 100 mL volumetric flask with 50 mL of acetate buffer. It was shaken for 30 min in a thermostatically controlled water bath. The volume was made up with the same buffer. The solution was filtered through 0.22 μm membrane filter, and 5 mL of the filtered solution was diluted with mobile phase in a 50 mL volumetric flask to produce a concentration of 10 μg/mL.

Validation of RP-HPLC Method

The method was validated according to the guidelines set on the International Conference on Harmonizaion (ICH) for the validation of the analytical procedures. The parameters, which were used to validate the method of analysis, were selectivity, linearity, range, accuracy, precision, limit of detection (LOD), limit of quantitation (LOQ), and robustness.

Selectivity was evaluated by comparing the chromatograms of rosiglitazone standard, tablet solution, and microsphere solutions. Triplicate injections of each were made. The UV spectra obtained from each sample was also compared.

The linearity response was assessed in the range of 5–100 μg/mL. Appropriate amounts of the stock solution were diluted with mobile phase, yielding concentrations of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, and 100 μg/mL. Triplicate injections of each were carried out. Peak areas of the standard solutions were plotted against their theoretical concentrations. The linearity was evaluated by calculation of the correlation coefficient obtained from linear regression analysis.

Limit of detection was determined based on standard deviation of the response and the slope as per ICH guidelines. The detection limit can be expressed as $LOD = 3.3\sigma/S$ where σ is the standard deviation of the response and S is the slope of the calibration curve.

The limit of quantitation (LOQ) was determined based on the standard deviation of the response (peak area) and the slope of the constructed calibration curve. The LOQ can be expressed as $LOQ = 10\sigma/S$.

The precision of the method applied to the tablets and microspheres was studied for the repeatability (intra-day assay) and intermediate precision (inter-day assay). Six sample solutions of RGM, equivalent to 20 μg/mL prepared from both tablets and microspheres, were analyzed during the same day under same experimental conditions. Intermediate precision was evaluated by analyzing the solutions on three different days. Peak areas were determined and compared. Precision was expressed as percentage relative standard deviation (RSD).

The accuracy of the method was evaluated by recovery test following standard addition method. Sample solution of RGM prepared from both tablets and microspheres with concentration of 20 μg/mL was spiked with three known concentrations of reference standard at three different levels lower, medium, and higher concentration. The recovery of the added reference standard was determined in triplicate and calculated by the following formula: $\%R = [(C_T - C_A)/C_R] \times 100$ in which, C_T is total concentration in spiked tablet/microsphere solution;

C_A is concentration in non-spiked tablet/microsphere solution; C_R is concentration of standard solution.

Analysis of Tablets and Determination of Encapsulation Efficiency of Rosiglitazone Maleate Microspheres

Samples prepared from the tablets and the microspheres were analyzed by the proposed RP-HPLC method. A theoretical concentration of 10 μg/mL sample prepared from tablets was injected for the analysis of the tablets in triplicate.

For the determination of the encapsulation efficiency of the microspheres, the sample solution with theoretical concentration of 10 μg/mL was injected. The drug encapsulation efficiency was determined using the following equation:

Drug encapsulation efficiency (DEE)

$$= [(\text{Theoretical drug content})/\text{Experimental drug content})] \times 100\%.$$

In-vitro Dissolution Test

Drug release studies were carried out according to the USP dissolution procedures for the single entity products using a paddle type 6-station dissolution test apparatus (TDT-06P, Electrolab, India), with stirring speed of 50 rpm in 500 mL of acetate buffer (pH 4.0) as dissolution medium under sink conditions. The temperature of dissolution medium was maintained at 37 ± 0.5°C. At each time interval, an exact volume of 10 mL sample was withdrawn and replaced immediately with identical volume of acetate buffer to maintain the sink condition. At predetermined time intervals (5, 10, 15, 20, 25, 30, 35, 40, 50, and 60 min) the concentrations of RGM in dissolution medium were determined by the proposed HPLC method. Dissolution test data were calculated based on the average of six parallel studies. The cumulative percentage drug released was plotted against time in order to obtain the dissolution release profile of RGM from tablets.

For the dissolution studies from microspheres a similar method was adopted. But the sample was withdrawn for 12 h at the time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h. The volume of sample withdrawn at different time intervals was 10 mL. The concentration of RGM was analyzed by the proposed HPLC method using the linear regression equation. The dissolution profile of the drug from the microspheres was obtained by plotting cumulative percentage drug released versus time.

RESULTS AND DISCUSSION

A reversed phase HPLC method was developed to obtain a specific procedure suitable for the rapid quality control analysis of RGM. Initially various mobile phase systems were prepared to achieve the best chromatographic condition comprising acetonitrile, methanol, ammonium acetate, acetate buffer, or their mixtures at different ratios with different flow rates. But the mobile phase comprised of acetonitrile: methanol: acetate buffer with pH 4.0 (30:20:50 v/v/v) was finally optimized to give retention time of 5.81 min for RGM. This mobile phase composition was found to be optimal for good peak shape and also to achieve minimal background current.

System suitability tests are an integral part of HPLC method development. These tests must be performed to ensure that the developed method can be able to produce results with acceptable accuracy and precision. The parameters, which were evaluated to perform the system suitability tests were column efficiency (N), peak symmetry (A_s), tailing factor (T), capacity factor (k), resolution (R_s), and retention time. Generally, at least two of these criteria are required to show that system suitability tests were carried out on freshly prepared standard stock solutions of rosiglitazone maleate. These parameters are shown in Table 1. The retention time of RGM standard sample, tablets solution, and solution from microspheres were 5.81, 5.81, and 5.71 min, respectively (Figs. 2, 3, and 4). The variation in the retention time among the six replicate injections of RGM reference solution was very little in raw materials, tablets, microspheres, showing the relative standard deviations (RSD%) of 0.295%, 0.677%, 0.209%. The linearity of the response was studied by linear regression analysis over the concentration range of 5–100 μg/mL. The plot of peak area versus concentration of the reference drug in the mobile phase and the spiked tablets and microsphere solutions were found to be linear in the range of 5–100 μg/mL. The correlation coefficient was calculated to be greater than 0.999. The calibration characteristics and the validation parameters

Table 1. HPLC system suitability test parameters

Peak symmetry (A_s)	0.951
Tailing factor (T)	1.097
Capacity factor (k)	2.631
Column efficiency (N^*)	540.097
Resolution (R_s)	5.6

*Column efficiency is expressed in terms of number of theoretical plates.

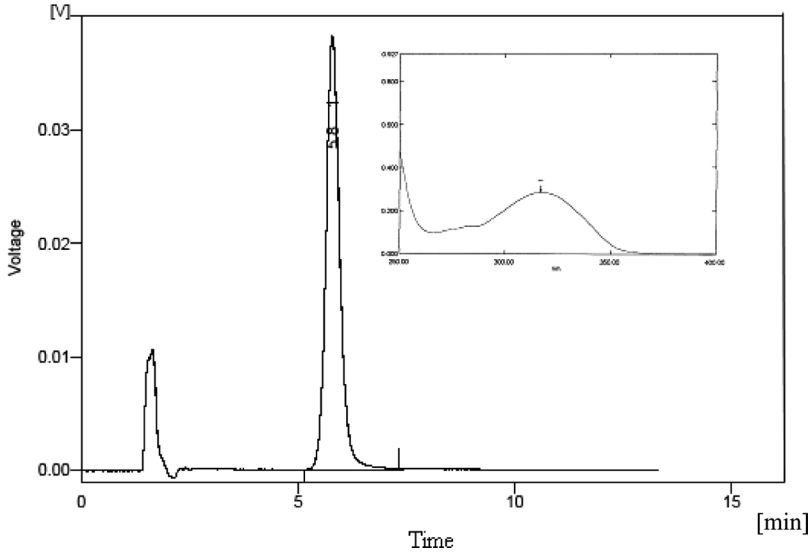

Figure 2. Typical chromatogram resulting from standard solution of rosiglitazone maleate. The insert shows the ultraviolet spectrum of the peak of rosiglitazone maleate, eluted at 5.81 min. RP-HPLC conditions: C8, 250 mm × 4.6 mm, acetonitrile: methanol: acetate buffer with pH 4.0 (30: 20: 50 v/v/v) mobile phase, 1.5 mL min^{-1} flow rate, UV detection 260 nm.

are shown in Table 2. The low values of SE of slope and correlation coefficient, greater than 0.999, showed the precision of the proposed method. Limit of detection (LOD) and limit of quantitation (LOQ) were determined according to the guidelines of ICH, based on the standard deviation of the response and the slope of the corresponding calibration curve.

The stability of the reference substance and the sample solutions from dosage forms were checked by analyzing a prepared standard solution kept at 4°C in the dark against a sample freshly prepared. The results of the analysis showed that there is no significant difference between freshly prepared sample and the sample aged 1 week. Neither the peak area nor the retention time of the drug changed considerably.

Accuracy, precision, and reproducibility of the proposed method were assessed by performing replicate analysis of the standard solutions in mobile phase. Within the linearity range, sample solutions obtained from tablets and microspheres were tested for the determination of intra-day and inter-day variability. The results of intra-day and inter-day variabilities were shown in Table 3, which shows good precision, accuracy, and reproducibility.

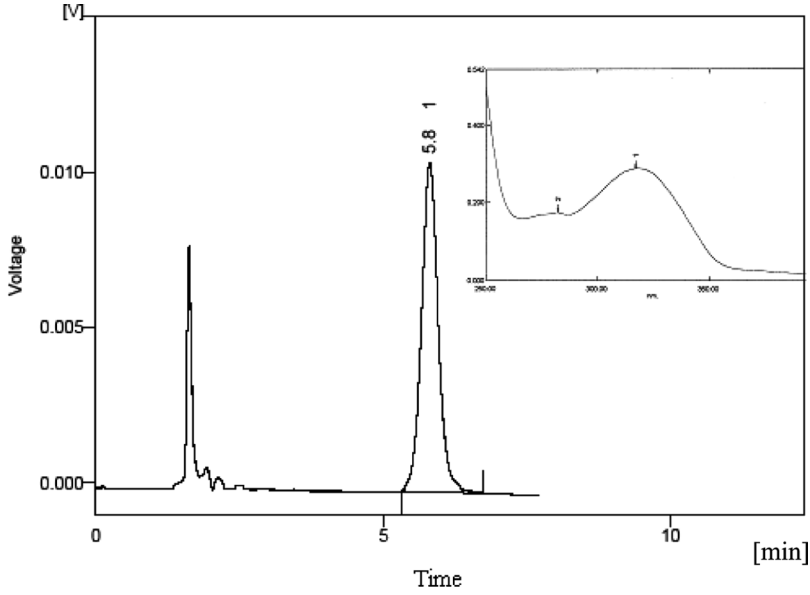

Figure 3. Typical chromatogram resulting from the assay of tablets of rosiglitazone maleate. The insert shows the ultraviolet spectrum of the peak of rosiglitazone maleate, eluted at 5.81 min.

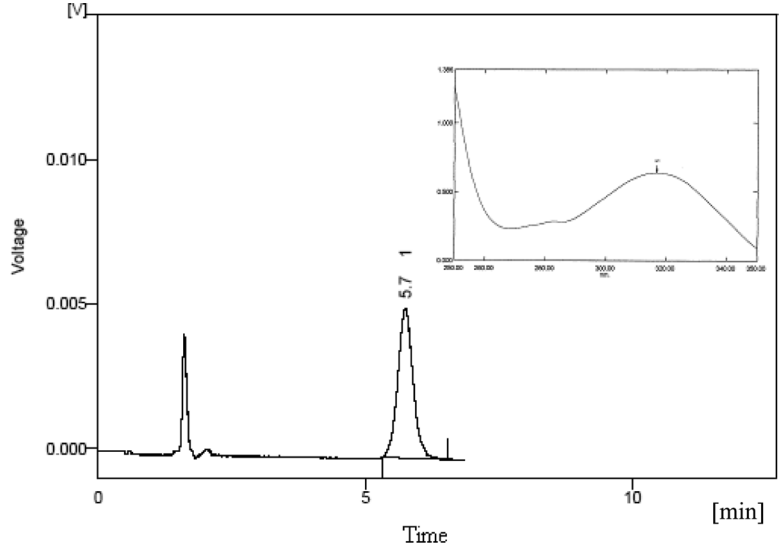

Figure 4. Typical chromatogram resulting from the assay or dissolution test of solutions of microspheres of rosiglitazone maleate. The insert shows the ultraviolet spectrum of the peak of rosiglitazone maleate, eluted at 5.71 min.

Table 2. Analytical parameters for the determination of Rosiglitazone maleate in mobile phase

Statistical Parameters	Values
Linearity range ($\mu g\,mL^{-1}$)	5–100
Slope ± standard error	8.0042 ± 0.0260
Intercept ± standard error	3.4381 ± 1.148
Correlation coefficient (r^2)	0.9999
Detection limit ($\mu g\,mL^{-1}$)	0.887
Quantitation limit ($\mu g\,mL^{-1}$)	2.688

The results of the analysis of tablets and the encapsulation efficiency of the microspheres by the proposed HPLC method are summarized in Table 4. The recovery study was carried out by using the standard addition method (Table 5). Recovery studies indicated the absence of interference from commonly encountered pharmaceutical excipients used in the selected formulation.

The proposed method was also applied to the dissolution study of RGM from tablets, as well as polymeric microspheres developed in our laboratory. RGM tablet formulation, Rezult® 4 containing 4 mg of the drug was investigated for dissolution studies using the paddle dissolution method. *In-vitro* dissolution testing is an integral part of pharmaceutical development and routine quality control monitoring of drug release characteristics. It can be considered as a very important testing tool to in-vivo drug bioavailability behavior. Hence this method can easily and conveniently be adopted for the routine quality control analysis of RGM from tablets and microspheres. The cumulative percentage drug released versus time was plotted to obtain the drug dissolution profile (Fig. 5 and 6). As it can be seen from the figures that more than 90% drug was released in the dissolution media within 15 min from tablets. But only 39.45% drug was released in 12 h from the microspheres. The release data were evaluated according to the different kinetic models namely zero order, first order, Hixson-Crowell, Higuchi,

Table 3. Intra-day and Inter-day precision of rosiglitazone maleate (standards) in mobile phase

Theoretical concentration ($\mu g/mL$)	Intra-day measured concentration ($\mu g/mL$)		Inter-day measured concentration ($\mu g/mL$)	
	Mean (%)	RSD (%)	Mean (%)	RSD (%)
50	99.72	0.9178	99.64	0.6423
10	100.79	0.9041	99.86	0.3381

Table 4. Results of the assay of rosiglitazone in tablets and microspheres

	Tablets (mg)	Microspheres
Drug content (mg)	4.00 (mg/tablet)	4.00*
Mean (%)	99.59	101.62**
RSD (%)	0.9452	1.6887

*Drug content is calculated on theoretical basis.
**indicates drug encapsulation efficiency of prepared microspheres.

Table 5. Results of recovery studies of rosiglitazone in tablets and microspheres

Formulation	Reference added ($\mu g mL^{-1}$)	Recovered ($\mu g mL^{-1}$)	Recovery (%)	Mean (%)	RSD (%)
Tablets (Rezult® 4)	5	4.95	99.02	99.60	0.5625
	10	9.96	99.64		
	20	20.02	100.14		
Microspheres	5	4.99	99.85	100.05	0.6265
	10	9.95	99.54		
	20	20.15	100.75		

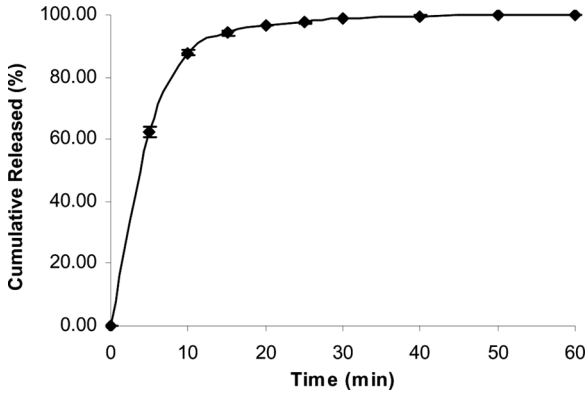

Figure 5. In-vitro dissolution profiles of rosiglitazone maleate tablets by proposed RP-HPLC method.

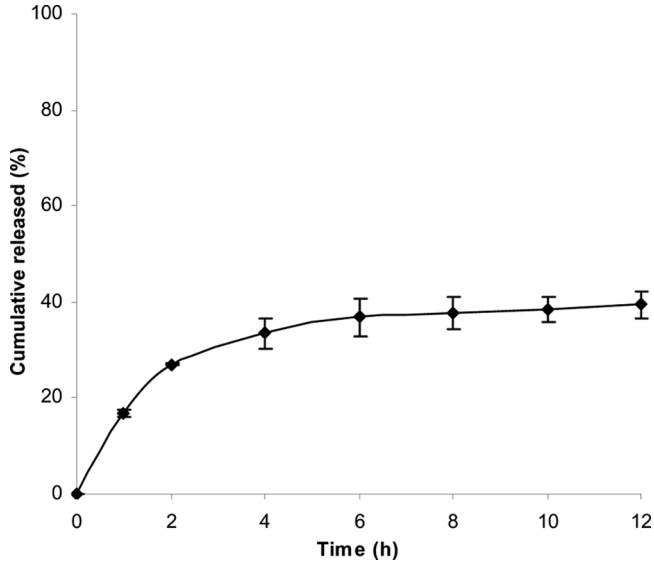

Figure 6. In-vitro dissolution profiles of microspheres of rosiglitazone maleate by proposed RP-HPLC method.

Table 6. Kinetic assessment of release data of rosiglitazone maleate tablets and microspheres*

Kinetic model	Parameter	Tablet	Microspheres
Zero order	k_{r0}	0.43730	0.02898
	r^2	0.44510	0.86688
First order	k_{r1}	−0.00042	−0.04930
	r^2	0.98650	0.88460
Hixon-Crowell	k_{HC}	−0.00053	0.02370
	r^2	0.82250	0.83470
Higuchi	k_H	1.08673	5.14950
	r^2	0.59170	0.93047
Peppas	k_p	0.55782	0.1578
	n	0.16170	0.1299
	r^2	0.71890	0.7837

*k_r, Release rate constant of first order kinetic; k_{r0}, Release rate constant of zero order kinetics; k_{HC}, Release rate constant of Hixson-Crowell kinetics; k_H, Release rate constant of Higuchi kinetics; k_p, Release constant of Peppas equation; r^2, Determination coefficient; n, Diffusional exponent.

and Korsemeyer-Peppas equation. All the kinetic data, related rate constants, and other parameters are presented in Table 6. For better understanding of the diffusion exponent (n) of the drug from tablets and microspheres, dissolution data were fitted to the Korsemeyer-Peppas equation where exponent *n* indicates the mechanism of release. The exponent value (*n*) was found to be 0.1617 and 0.1299 for dissolution of the drug from tablets and microspheres, respectively. From the kinetic data of Table 6, it can be assumed that drug release followed first order kinetics from tablets and Higuchi kinetics from microspheres. The release of RGM from the tablets was completed within 60 min in the proposed method.

CONCLUSION

An isocratic and fast RP-HPLC method was developed and validated to determine rosiglitazone maleate in tablets, polymeric microspheres, and their dissolution studies. The method employed a mobile phase composed of acetonitrile: methanol: acetate buffer with pH 4.0 (30:20: 50 v/v/v) with a total elution time less than 6 min. The method showed linearity, precision, accuracy, and selectivity regarding excipients present in the tablets and microspheres. This rapid method is feasible to determine rosiglitazone in the quality control for routine assay, content uniformity study, and also for dissolution tests of tablets, as well as microspheres containing rosiglitazone maleate.

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