Biorelevant and Quality Control Dissolution Method Development and Validation of Quetiapine Fumarate Tablets

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ABSTRACT

The aim of this study was to develop and validate Biorelevant and Quality control dissolution method for poorly water soluble drug Quetiapine Fumarate (QF). The Ultra Violet spectrophotometric method developed was based on the direct estimation method using 248 nm as λmax. The method was validated according to International Conference on Harmonization (ICH) guidelines which include precision, specificity, accuracy and linearity. The Biorelevant dissolution medium i.e., Blank Fed State Simulated Intestinal Fluid (FeSSIF) and Quality control dissolution medium i.e., 0.1N Hydro Chloric acid were selected on the basis of solubility studies. Stability studies were performed in respective dissolution mediums and the sample solutions were found to be stable for 2 days. The corresponding Biorelevant and Quality control dissolution profiles were constructed and the selected brands showed more than 85% drug release within 20 min. Thus, the proposed Biorelevant and Quality control dissolution methods can be used successfully.

Keywords: Biorelevant, Dissolution, Quetiapine fumarate, UV spectrophotometry, Validation.

INTRODUCTION

Dissolution is a required performance test for solid dosage forms, transdermal patches and suspensions. It is also only test that measures the rate of *in vitro* drug release as a function of time, which can reflect either reproducibility of the product manufacturing process or, in limited cases, *in vivo* drug release. It is an important tool in drug development and quality control [1]. Dissolution

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test that can predict the *in vivo* performance of drug products are usually called biorelevant dissolution tests. These tests can be used to guide formulation development, to identify food effects on the dissolution and bioavailability of orally administered drugs, and to identify solubility limitations and stability issues[2]. Chemically quetiapine fumarate is 2-[-2(4-Dibenzo [b,f] [1.4] thiazepin-11-yl-1-piperazinyl) ethoxy] ethanol fumarate salt.[3] (Shown in Figure 1)
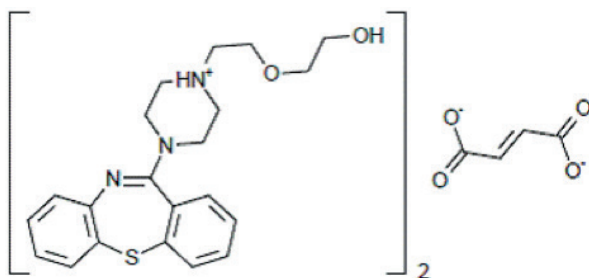

Figure 1. Chemical structure of Quetiapine fumarate.

Its molecular formula is $2(C_{21}H_{25}N_3O_2S).C_4H_4O_4$. QF appears as white crystalline solid and can be stored at room temperature[4]. It is an atypical antipsychotic drug, used in the treatment of psychosis associated with Parkinson's disease, chronic schizophrenia[5] and bipolar disorders[6]. The dibenzothiazepine structure with two basic nitrogen atoms is responsible for its higher solubility under acidic conditions. At a pH above 4, the water solubility is poor; towards pH 2, an increase in solubility is noticeable. Due to its poor solubility over the physiological pH range but because of its high permeability, quetiapine is classified as a Biopharmaceutics Classification System class II drug.[7] Quetiapine's antipsychotic activity is likely due to a combination of antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Antagonism at D2 receptors relieves positive symptoms while antagonism at 5HT2A receptors relieves negative symptoms of schizophrenia.[8] In the present investigation an attempt was made to develop and validate a simple Biorelevant and quality control dissolution method for QF with greater precision and accuracy.

MATERIALS AND METHODS

Materials

Quetiapine fumarate pure drug was received as a gift sample for analyzing using UV spectrophotometry technique.[9, 10, 11] Sodium Chloride, Glacial Acetic acid, Sodium taurocholate, lecithin, methylene blue, hydrochloric acid (HCl) and Sodium hydroxide pellets were procured from SD Fine Chem LTD (Mumbai). All reagents and solvents used were of Analytical grade. The commercial products

of QF that is Quitipin®, Qutan®, Quel® were procured from local drug stores. Dissolution apparatus USP type II (USP model: TDT-06P, Electrolabs, India) and UV Spectrophotometer (UV model 1700, Shimadzu, Japan) were used.

Methods

Solubility Studies

Solubility data was used as the basis for the selection of the best solvent for dissolution of Quetiapine fumarate tablets. It was expressed as amount of drug dissolved. For equilibrium solubility studies, excess of the drug was placed in 25 ml beakers containing different media: Distilled water, 0.1N HCl (pH 1.2), pH 4.5 Acetate buffer, pH 6.5 Phosphate buffer, pH 7.4 Phosphate buffer and Blank Fed State Simulated Intestinal Fluid (FeSSIF). The samples were gently rotated in water bath shaker at $37 \pm 0.5°C$ for 24 h. An aliquot (2 ml) was removed from each beaker after 24 h and filtered using 0.45 μm syringe filter. 1 ml of filtered samples were diluted with corresponding medium and analyzed by UV spectrophotometry at corresponding λ_{max}.

Stability studies

Stability studies were performed by preparing solutions of pure drug mixture and commercial products of the drug and preserving it for 2 days. An accurately weighed quantity of pure drug and tablet powder were dissolved in sufficient quantity of 0.1N HCl and Blank FeSSIF to get the final stock concentration. An aliquot of these stock solutions was diluted with 0.1N HCl and Blank FeSSIF to get the final concentration of 10 μg/ml. All the solutions were prepared in three replicates. The solutions were kept at $37 \pm 0.5 °C$ for 1 h under light shaking, later being left at room temperature for 48 h. Aliquots of samples were analyzed spectrophotometrically after 1 h, 24 h and 48 h.[12]

Preparation of 0.1N HCl

Conc. HCl (85 ml) was dissolved in 1 L of distilled water to get 0.1N HCl solution.

Preparation of blank fed state simulated intestinal fluid (FeSSIF)

Blank FeSSIF (pH 5.0) was prepared by dissolving 11.874 g of sodium chloride, 8.65 g (8.238 ml) of glacial acetic acid and 4.04 g of sodium hydroxide pellets in 1 L of distilled water.

Preparation of fed state simulated intestinal fluid

FeSSIF was prepared by dissolving 8.25 g of sodium taurocholate in 250 ml of blank FeSSIF, 29.54 ml of a solution containing 100 mg/ml lecithin in methylene chloride is added to form an emulsion, and then methylene chloride is

eliminated under vacuum until a clear, micellar solution having no perceptible odor of methylene chloride is obtained. After cooling to room temperature, the volume is adjusted to 1 L with blank FeSSIF.

Quality Control Dissolution Method Development and Validation

UV Method Development & Determination of λ max

An accurately weighed quantity of QF was dissolved in suitable volume of 0.1N HCl to prepare the stock solution. An aliquot from this stock solution was diluted with 0.1N HCl to get a final concentration of 10µg/ml. All solutions were prepared in three replicates. The above solutions were scanned in the range of 200-400 nm in 1.0cm cell against 0.1N HCl and spectra were recorded to determine the λ_{max} of the drug. Figure 2 shows the UV absorption spectra of QF.

Preparation of standard solutions and calibration curve

Stock solution of QF was prepared by dissolving an accurately weighed quantity of QF in 0.1N HCl. From the stock solution various concentrations i.e., 1, 2, 3, 4, 5, 6, 7, 10, 15, 20 and 25 µg/ml were prepared. All solutions were scanned in wavelength range of 200-400 nm. The absorbance was plotted against the respective concentrations to obtain the calibration curve. The spectrum showing linearity of QF is given in Figure 3. The calibration data is shown in Table 3 and curve in Figure 4.

Validation Parameters

Validation of the proposed methods was carried out for its linearity & range, accuracy, specificity and precision according to ICH guidelines.[13, 14]

Linearity and Range

For the determination of linearity of QF in commercial products, sample solutions of different concentrations were prepared. The stock solution of QF for all the three brands were prepared by dissolving required amount of QF in suitable volume of 0.1N HCl. The solution was sonicated for 10 min and then filtered through Whatman filter paper. The solutions were further diluted to get concentrations in range of 1 – 25 µg/ml.

The absorbance of the above solutions was measured at 248 nm. A graph of absorbance v/s concentration was plotted and correlation coefficient is calculated. The linearity data for all the three brands is presented in Table 4. The graphs were constructed as concentration v/s absorbance and depicted in Figure 5 to Figure 7.

Acceptance criteria: Correlation coefficient should be within 0.997 – 0.999.

Accuracy

The accuracy was determined by performing recovery studies at three different concentration levels i.e., 50%, 100%, 150% in triplicate. The individual recovery and mean recovery values were calculated and are shown in Table 5 to 7 for all three brands.

Preparation of sample solutions:

Sample preparation of 50%: Tablet powder equivalent to 50 mg of QF and 25 mg of QF Active Pharmaceutical Ingredient were taken in 100 ml volumetric flask. Sufficient quantity of 0.1N HCl was added and sonicated to dissolve it and the volume was made up to the mark. Then the solution was filtered through Whatman filter paper and appropriate dilutions of 5, 10 and 15 µg/ml were prepared. The absorbance of final solutions was measured at 248 nm.

Sample preparation of 100%: Tablet powder equivalent to 50 mg of QF and 50 mg of QF API were taken in 100 ml volumetric flask. Sufficient quantity of 0.1N HCl was added and sonicated to dissolve it and the volume was made up to the mark. Then the solution was filtered through Whatman filter paper and appropriate dilutions of 5, 10 and 15 µg/ml were prepared. The absorbance of final solutions was measured at 248 nm.

Sample preparation of 150%: Tablet powder equivalent to 50 mg of QF and 75 mg of QF API were taken in 100 ml volumetric flask. Sufficient quantity of 0.1N HCl was added and sonicated to dissolve it and the volume was made up to the mark. Then the solution was filtered through Whatman filter paper and appropriate dilutions of 5, 10 and 15 µg/ml were prepared. The absorbance of final solutions was measured at 248 nm.

The absorbance of the standard solutions of 50%, 100% and 150% were measured. From this individual recovery and mean recovery values were calculated.

Acceptance criteria: The % recovery for each level should be between 98.0 to 102.0%.

Specificity

The specificity of test method was established by comparing the spectra of the sample solutions of same concentration of pure drug and commercial products. The similarity in spectra was shown in Figure 8.

Precision

The precision was determined by studying repeatability and intermediate precision. The stock solution of QF for all the three brands were prepared by dissolv-

ing an accurately weighed quantity of QF in sufficient volume of 0.1N HCl and sonicated for 10 min. The sample solution was then filtered through Whatman filter paper. The solution was further diluted to get 5 and 10 µg/ml solutions. All dilutions were prepared in triplicate.

Repeatability

To check repeatability, the samples of concentrations 5 µg/ml and 10 µg/ml were analyzed at 248 nm on same day and under same experimental conditions. % RSD was calculated and is shown in Table 8.

Intermediate precision (Interday and Intraday precision)

The interday precision was determined by analyzing the sample solutions of concentration 5 µg/ml and 10 µg/ml at 248 nm on different days under same experimental conditions. % RSD was calculated is shown in Table 9.

The intraday precision was determined by analyzing the sample solutions of concentration 5 µg/ml and 10 µg/ml at 248 nm, in two different laboratories on the same day. % RSD was calculated is shown in Table 10.

Quality Control Dissolution Method Development

The best dissolution medium was selected on the basis of the solubility studies. Various dissolution conditions were tested for the development of a suitable dissolution method for the dissolution of QF tablets. The following dissolution conditions were selected and the analytical method used was UV spectrophotometry.

Medium: 0.1N HCl

Volume : 900 ml

Apparatus: USP Type II (Paddle Apparatus)

RPM: 50

Temperature: 37 ± 0.5 °C

Time interval: 10, 20, 30, 45 min.

Preparation of test solution

A tablet was placed in each vessel of the six dissolution vessels of the tablet Dissolution Tester USP (Electrolab, India) containing 0.1N HCl dissolution medium after testing sink conditions. A 5 ml aliquot of the sample was withdrawn at 10, 20, 30, 45 min intervals replacing 5 ml of dissolution medium each time. The samples were filtered through Whatman filter paper.

Analysis of the dissolution samples

The filtered dissolution samples were analyzed spectrophotometrically and % drug release was calculated and shown in Table 11. The graph of percentage drug release versus time is shown in Figure 9.

Acceptance criteria: All the 6 tablets must show % drug release of more than 85%.

Biorelevant Dissolution Method Development

Based on solubility and stability studies the dissolution parameters includes Blank FeSSIF (900 ml) as medium in USP Type II (Paddle Apparatus) with 50 RPM maintained at temperature of 37 ± 0.5°C. A tablet was placed in each vessel of the six dissolution vessels after testing sink conditions. A 5 ml aliquot of the sample was withdrawn at 10, 20, 30, 45 min intervals replacing 5 ml of dissolution medium each time. The samples were filtered through Whatman filter paper. The Biorelevant dissolution samples were analyzed by UV spectrophotometry and % drug release was calculated and shown in Table 11. The graph of % drug release vs. time is shown in Figure 10.

Acceptance criteria: All the 6 tablets must show % drug release of more than 85%.

RESULTS AND DISCUSSION

Solubility studies

The solubility studies were performed in different media by placing excess of drug in the medium and gently shaking it for 1 h. The samples were collected and analyzed spectrophotometrically after 24 h. The results of solubility studies are given in Table 1. The drug is found to be soluble in 0.1N HCl and Blank FeSSIF. So it was selected as dissolution medium.

Solvent	Solubility (mg/ml)
Distilled water	3.3
0.1N HCl	35.6
Acetate buffer pH 4.5	5.8
Phosphate buffer pH 6.8	2.1
Phosphate buffer pH 7.4	1.3
Blank FeSSIF	9.2

Table 1. Solubility data of QF in different media

Stability Studies

The stability studies were performed by analyzing sample solution of concentration 10 µg/ml prepared by appropriate dilutions from the stock solution of pure drug and tablet formulations of QF and preserving for 2 days. All samples were prepared in triplicate, the results of stability studies are given in Table 2. It was found that the sample solutions of QF are stable for 48 h at room temperature.

Absorbance											
Stability data of QF in 0.1N HCl						Stability data of QF in Blank FeSSIF					
Pure drug			Commercial product			Pure drug			Commercial product		
1 h	24 h	48 h	1 h	24 h	48 h	1 h	24 h	48 h	1 h	24 h	48 h
0.474	0.481	0.487	0.409	0.411	0.415	0.355	0.359	0.348	0.463	0.467	0.471
0.477	0.486	0.491	0.413	0.414	0.417	0.356	0.361	0.369	0.465	0.467	0.469
0.474	0.482	0.490	0.410	0.409	0.412	0.358	0.363	0.368	0.461	0.465	0.473

Table 2. Stability data of QF in 0.1N HCl and Blank FeSSIF

UV Method Development and Determination of λ_{max}

Diluted samples of concentration 10 µg/ml were prepared in triplicate from standard solution of QF. The samples were scanned in the range of 200-400 nm in 1.0 cm cell against 0.1N HCl. Figure 2 shows the UV absorption spectrum of QF. λ_{max} of QF was found to be 248 nm.
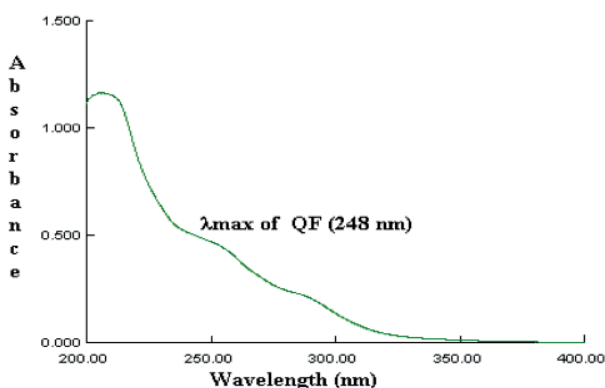

Figure 2. UV absorption spectrum of Quetiapine fumarate

The calibration curves of QF in 0.1 N HCl were constructed and were found to be linear. Beer's law was obeyed in the concentration range of 1 to 25 µg/ml for QF in 0.1 N HCl. The UV spectrum for the linearity of QF is shown in Figure 3 and the calibration curve is shown in Figure 4 with data given in Table 3.
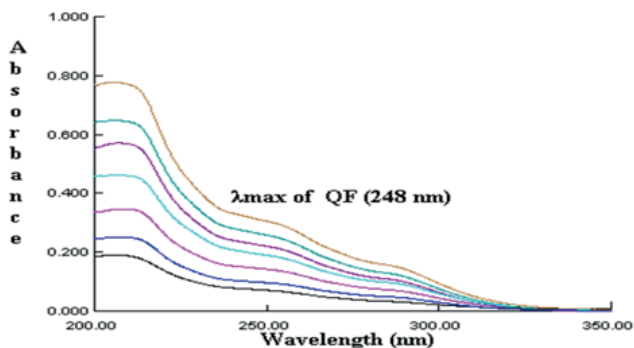
Figure 3. Linearity of QF at different concentration levels

Serial No.	Concentration (µg/ml)	Absorbance (Mean ± SD)
1	1	0.072 ± 0.02
2	2	0.098 ± 0.02
3	3	0.144 ± 0.01
4	4	0.193 ± 0.04
5	5	0.234 ± 0.02
6	6	0.272 ± 0.02
7	7	0.342 ± 0.01
8	10	0.479 ± 0.05
9	15	0.688 ± 0.02
10	20	0.902 ± 0.01
11	25	1.161 ± 0.04

Table 3. Result of Calibration data for QF
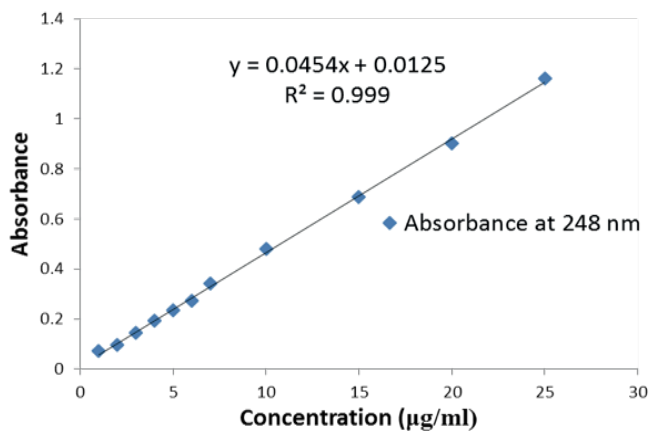
Figure 4. Calibration curve of QF Pure drug

VALIDATION

Linearity and Range

The proposed method was found to linear in the range of 1 - 25 µg/ml for the three brands.The graphs were constructed as concentration vs. absorbance and are depicted in Figure 5, 6 & 7. The linearity data is given in Table 4 for QF in all the three brands.

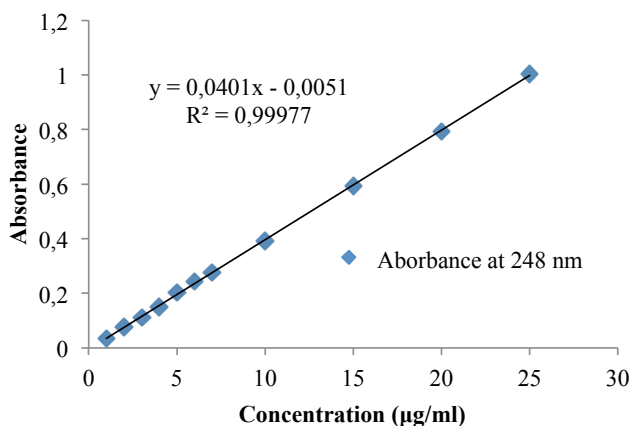Beer's law was obeyed in concentration range of 1 µg/ml to 25 µg/ml for Quitipin®, Qutan®&Quel®.
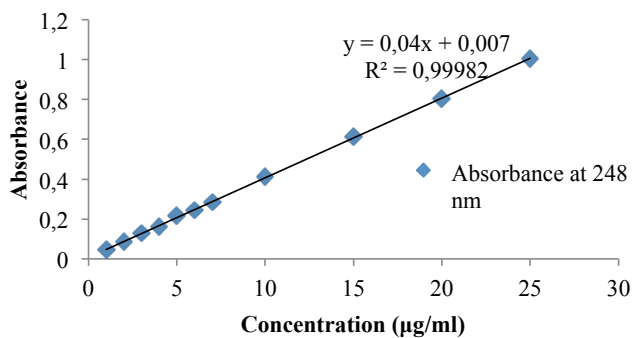

Figure 5. Linearity curve of QF in Quitipin®
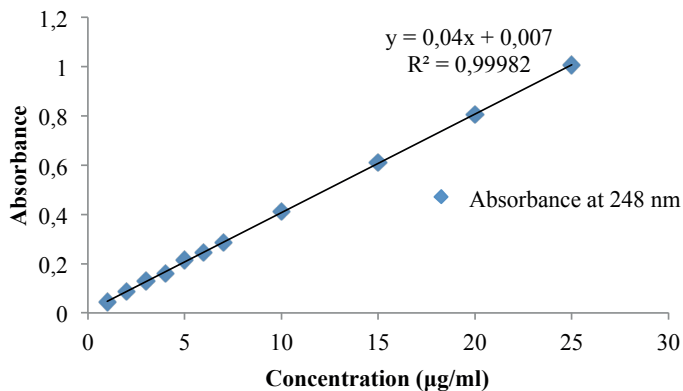

Figure 6. Linearity curve of QF in Qutan®

Figure 7. Linearity curve of QF in Quel®

Serial No.	Concentration (µg/ml)	Absorbance (Mean ± SD)		
		Quitipin®	Qutan®	Quel®
1	1	0.035 ± 0.01	0.044 ± 0.03	0.044 ± 0.02
2	2	0.077 ± 0.01	0.087 ± 0.02	0.081 ± 0.02
3	3	0.112 ± 0.02	0.130 ± 0.02	0.128 ± 0.01
4	4	0.150 ± 0.04	0.160 ± 0.04	0.163 ± 0.02
5	5	0.203 ± 0.02	0.214 ± 0.02	0.198 ± 0.04
6	6	0.242 ± 0.02	0.244 ± 0.01	0.245 ± 0.01
7	7	0.276 ± 0.01	0.286 ± 0.01	0.290 ± 0.03
8	10	0.392 ± 0.04	0.412 ± 0.02	0.410 ± 0.05
9	15	0.593 ± 0.03	0.611 ± 0.05	0.624 ± 0.04
10	20	0.793 ± 0.01	0.804 ± 0.03	0.822 ± 0.02
11	25	1.004 ± 0.02	1.006 ± 0.02	1.016 ± 0.01

Table 4. Results for the linearity reading of QF in Quitipin®, Qutan®&Quel®

Accuracy

The recovery studies were performed for QF at three different concentration levels i.e., 50%, 100%, 150% in triplicate. The individual recovery and mean recovery values were calculated and are shown in Table 5 to 7 for all the three brands. The % recovery was under the acceptance criteria of 98% to 102%. Thus, the method is accurate.

% Conc. at specific levels	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD
50%	25	25.22	100.90	100.50 ± 0.61
	25	24.95	99.80	
	25	25.20	100.80	
100%	50	49.80	99.60	99.45 ± 0.21
	50	49.76	99.53	
	50	49.61	99.21	
150%	75	75.62	100.82	100.03 ± 0.70
	75	74.84	99.78	
	75	74.63	99.50	

Table 5. Results of Recovery studies of Quitipin®

% Conc. at specific levels	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD
50%	25	25.00	99.99	100.02 ± 0.07
	25	25.03	100.10	
	25	25.00	99.98	
100%	50	49.43	98.86	99.12 ± 0.40
	50	49.79	99.58	
	50	49.46	98.91	
150%	75	75.02	100.02	100.36 ± 0.47
	75	75.68	100.90	
	75	75.12	100.16	

Table 6. Results of Recovery studies of Qutan®

% Conc. at specific levels	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD
50%	25	25.03	100.12	100.10 ± 0.11
	25	25.05	100.20	
	25	25.00	99.99	
100%	50	50.55	101.10	101.07 ± 0.07
	50	50.50	100.99	
	50	50.56	101.12	
150%	75	74.24	98.98	99.56 ± 0.50
	75	74.86	99.81	
	75	74.92	99.89	

Table 7. Results of Recovery studies of Quel®

Specificity

The method was confirmed to be specific by analyzing samples of pure drug and commercial products. It was observed that there was no interference of the excipients. (Represented in Figure 8)
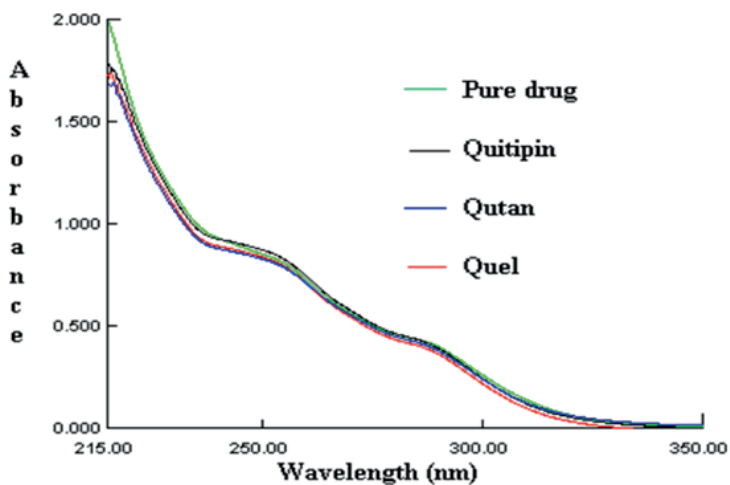
Figure 8. Spectra of pure drug and commercial products

Precision

The precision was determined by Repeatability (Table 8), Inter day (Table 9) and Intraday precision (Table 10) and the % RSD was found to be less than 2% for all the three brands.

The low %RSD values indicate that the method is precise.

Brand	Concentration prepared (µg/ml)	Concentration* (µg/ml)	% RSD
Quitipin®	5	5.13 ± 0.04	0.74
	10	10.05 ± 0.02	0.25
Qutan®	5	4.78 ± 0.02	0.52
	10	10.14 ± 0.07	0.71
Quel®	5	4.64 ± 0.04	0.80
	10	9.86 ± 0.09	0.87

Table 8. Results for Repeatability

Brand	Concentration prepared (µg/ml)	Concentration* (µg/ml)		% RSD	
		Day 1	Day 2	Day 1	Day 2
Quitipin®	5	5.13 ± 0.04	4.77 ± 0.02	0.74	0.52
	10	10.05±0.02	9.55 ± 0.07	0.25	0.69
Qutan®	5	4.78 ± 0.02	5.11 ± 0.03	0.52	0.57
	10	10.14±0.07	10.12±0.05	0.71	0.51
Quel®	5	4.64 ± 0.04	4.57 ± 0.04	0.80	0.82
	10	9.86 ± 0.09	9.65 ± 0.09	0.87	0.96

Table 9. Results for Intermediate Precision (Interday)

Brand	Concentration prepared (µg/ml)	Concentration* (µg/ml)		% RSD	
		Lab 1	Lab 2	Lab 1	Lab 2
Quitipin®	5	5.13 ± 0.04	5.02 ± 0.04	0.74	0.76
	10	10.05±0.02	10.00±0.09	0.25	0.86
Qutan®	5	4.78 0.02	4.83 0.02	0.52	0.52
	10	10.14 0.07	9.90 0.05	0.71	0.51
Quel®	5	4.64 ± 0.04	4.85 ± 0.02	0.80	0.50
	10	9.86 ± 0.09	9.95 ± 0.05	0.87	0.51

Table 10. Results for Intermediate Precision (Intraday)

Quality Control and Biorelevant Dissolution Method Development

The filtered Quality control dissolution samples & Biorelevant dissolution samples were analyzed spectrophotometrically and % drug release was calculated and shown in Table 11.The graph of % drug release versus time is shown in Figure 9 & Figure 10 respectively.By employing the optimized conditions for dissolution, % drug release of more than 85% was achieved within 20 min for all the three brands.

Time (mins)	% Drug release* (Mean ± SD)					
	Dissolution of QF in commercial products			BioRelevant Dissolution of QF in commercial products		
	Qutipin®	Qutan®	Quel®	Qutipin®	Qutan®	Quel®
10	78.66 ± 2.1	77.58 ± 2.5	75.96 ± 4.1	75.4 ± 2.6	72.72 ± 3.1	77.94 ± 2.7
20	93.42 ± 3.2	92.7 ± 3.3	90.18 ± 3.9	86.8 ± 2.1	87.48 ± 3.4	89.28 ± 3.2
30	97.56 ± 2.5	95.04 ± 3.8	94.68 ± 4.6	94.3 ± 3.7	94.14 ± 4.0	96.48 ± 3.7
45	101.2 ± 3.2	100.8 ± 4.1	100.5 ± 3.5	98.92 ± 3.5	98.28 ± 3.6	100.8 ± 2.5

Average of 6 determinations

Table 11. Results for Dissolution and Biorelevant Dissolution of commercial products
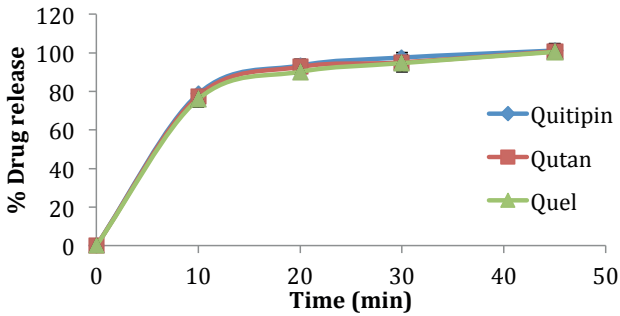
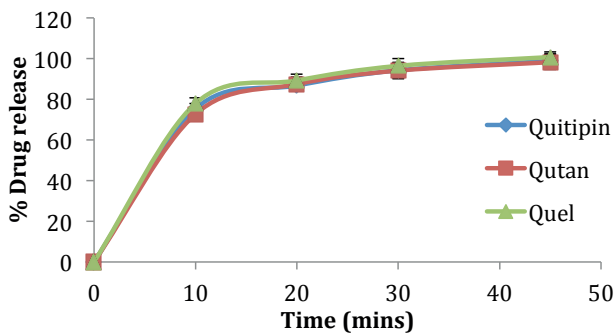**Figure 9.** Dissolution profile of QF in commercial products.

Figure 10. Biorelevant Dissolution profile of QF in commercial products.

CONCLUSION

Biorelevant and quality control dissolution methods were developed and validated. The best dissolution medium selected on the basis of solubility studies for quality control dissolution was 0.1N HCl and the medium for biorelevant dissolution was Blank FeSSIF. The stability studies were performed and the sample solutions were found to be stable for 2 days. The analytical method developed was UV spectrophotometric method involving direct estimation method for QF. The λmax of QF was found to be 248 nm. The method was validated for various parameters like linearity, precision, accuracy and specificity. All the parameters were found to be under the acceptance criteria. The quality control dissolution profile and Biorelevant dissolution profile was obtained by using 900 ml of dissolution medium containing 0.1N HCl and Blank FeSSIF respectively maintained at 37° ± 0.5 °C with paddle apparatus at 50 rpm for 45 min. More than 85% of the drug was released within 20 min. Thus, the methods developed were precise, accurate and reproducible and can be employed as quality control and biorelevant method.

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