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ORIGINAL ARTICLE

Pharmaceutical Equivalence Studies of Different Brands of Sparfloxacin 100 mg Tablets Available in Pakistani Market

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Authors' Contributions
1 Conception & Study Design, Data Collection, Data Analysis.
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ABSTRACT

***Objective*:** The comparative study has been designed to evaluate the quality and physicochemical characteristics of five different Sparfloxacin (100 mg) tablet brands.

***Methods*:** A quality control assessment by different quality parameters and cost effective comparative pharmaceutical equivalence studies were conducted on five brands of Sparfloxacin 100 mg tablets. These brands were coded as S-1, S-2, S-3, S-4 and S-5 and their prices were 678.01, 325, 400, 300 and 199 rupees per pack, respectively. Statistical calculation (ANOVA) and similarity factor (f_2) were also applied to compare the results of different brands.

***Results*:** Results of physical and chemical parameters of all brands were found satisfactory. Similarly, the value of f_2 showed that brand S-2 was found to be very similar with reference (S-1) while other brands also showed similarity.

***Conclusion*:** This study would be helpful for the physicians and pharmacists for the selection of cost-effective and quality product for the treatment of variety of bacterial infections such as urinary tract infection, respiratory tract infection, ear infection and skin infections.

Keywords: Sparfloxacin, brand comparison, similarity factor, HPLC.

INTRODUCTION

A fluorine atom is present in the fluoroquinolones antibiotics, at the position of carbon 6 or 7 of the central ring system [1]. Sparfloxacin, a third-generation quinolone antibiotics, having broad spectrum activity against gram-positive and gram-negative microorganisms as well as against anaerobes, atypical pathogens and some *bacteroides fragilis* group [2-4]. It is structurally 5-amino-1 cyclopropyl-7-(*cis*-3, 5-dimethyl)-1-piperozinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3 quinoline. Approximately, 45% of sparfloxacin bound to serum proteins, with 20 ± 4 h half-life [5]. It has splendid bioavailability (92%) as compare to other fluoroquinolones derivatives. It is recommended in the management of diabetic foot

infections, respiratory tract infections and tuberculosis [6]. An inadequate quality of drugs are being used in many under developed countries. Utilization of low-quality medicines in some cases, resulted in the management failure [7]. The low quality of drugs has been connected to counterfeiting of medicines, chemical instability notably in tropical climates [8] and less quality control during manufacturing [9]. Drug regulatory authority of Pakistan has granted marketing authorization of different medicines for public use on the behalf of limited clinical trials and literature review information [10]. Different therapeutic responses have been observed in marketed products while each contained same active pharmaceutical ingredients [11]. Furthermore, variation in price of different brands of same generic drugs results in significant variation in quality of products [12]. Due to these facts, increasing cases of morbidity, mortality and patient's non-compliance due to substandard and counterfeit medicines have been observed [13]. The outcomes of a report, prepared by the pharmacy department, University of Nairobi, indicated that 46% of locally produced items for consumption were unsatisfactory when active ingredient was quantified by compendia schemes [14].

Moreover, Pakistan is also included among those countries which are listed for the largest importer of counterfeit drugs [15]. Therefore, it is necessary to access the quality of distinct brands by conducting post-marketing surveillance in Pakistan and to evaluate the cost effectiveness of antibiotic medicines in local health care setups. Different researchers have reported the comparison of quality control parameters of different brands [16-19]. However, no study is available on the comparison of sparfloxacin brands marketed in Pakistan. Therefore, the present research work was conducted to assess and compare the quality control parameters of sparfloxacin (100 mg) tablets available in different pharmacies and hospitals of Karachi. The quality was assessed in terms of thickness, breaking force, uniformity of weight, disintegration time, *in vitro* drug release and sparfloxacin content. Furthermore, the achieved parameters were compared with the standards of United State and British Pharmacopeias. This study will be useful in cost effective therapy by selecting low cost brand having same quality standards.

MATERIALS AND METHODS

Materials

Sparfloxacin reference standard was a kind gift of M/S Abbott Laboratories Pakistan Limited. Analytical grade acetonitrile and methanol were procured from Merck (Darmstadt, Germany). Sodium acetate, acetic acid glacial, and sodium hydroxide were procured from Sigma-Aldrich (St. Louis, MO, USA). Highly purified water (18 MΩ•cm) was prepared by processing de-ionized (DI) water through a PureLab Ultra System (ELGA, UK). All other chemicals utilized in the experiment were of analytical grade.

Sample Collection

Five different brands of sparfloxacin (100 mg) tablets were collected from various pharmacies of hospitals located at Karachi. All the brands were within the expiry date during the study and were assigned specific codes as S-1, S-2, S-3, S-4 and S-5. The detail information of all brands are given in Table **1**.

Table 1. Labeling information of five brands of sparfloxacin 100 mg tablets.

Brand Code	Manufacturing Date	Expiry Date	Retail Price Per Pack (PKR)
S-1	02-2017	02-2019	678.01
S-2	05-2016	04-2019	325
S-3	06-06-2016	06-06-2018	400
S-4	11-2016	11-2019	300
S-5	02-2016	02-2019	199

Quality Control Assessment of Brands

The quality control parameters of the collected brands were assessed regarding, uniformity of weight, tablet breaking force, friability, disintegration time, *in vitro* drug release study and sparfloxacin content tests.

Uniformity of weight test

Randomly, twenty tablets of each brand were selected and weighed individually using analytical weighing balance (ID # QB6228EA, Scientech SP250). The test was conducted as per official method (USP). The weight of each tablet was recorded in milligrams (mg). The percentage weight variation was calculated using the Microsoft Excel (2010).

Thickness test

Using digital Varnier Caliper, thickness of 20 tablets was calculated and the values were noted in millimeters (mm). The data was analyzed statistically using control chart.

Out of 20 tablets, only 2 tablets were allowed to cross the limits of ± 5%. However, upper and lower control limits were calculated by using the following formulas:

Upper control limit (UCL = Mean + (3 × standard deviation) ---------- Eq. 1

Lower control limit (LCL) = Mean - (3 × standard deviation) ---------- Eq. 2

Tablet breaking force test

Commonly the term breaking force of tablets is also called hardness test, which represents the true picture of the test more accurately than hardness, because tablets are actually crushed during the test (USP32–NF27). The breaking force of tablets was carried out on 20 tablets by using Dr. Schleuniger tablet hardness tester (ID #QHT 6235EA). The hardness values were recorded in Strong Cobb (SC). Out of 20 tablets, only 2 tablets were permitted to cross the limit of NLT 5.0 SC. Upper and lower control limits were determined by using the following formulas:

UCL = Mean + (3 × standard deviation) ---------- Eq. 3

UCL = Mean - (3 × standard deviation) ---------- Eq. 4

Friability test

For friability, twenty tablets were accurately weighed and transferred into the friabilator (Varian QR1336QA, Germany). Briefly, tablets were exposed to rolling and abrasion in a plastic chamber which rotates for 100 revolution. Then, the tablets were again weighed and the loss in weight indicated the fragility. Friability were assessed by using equation 5.

$$Friability\ (\%) = \frac{(Initial\ Weight\text{-}Final\ Weight)}{Initial\ Weight} \times 100$$

---------- Eq. 5

Limits: Percentage friability less than 1% is considered acceptable (USP).

Disintegration time

The disintegration test was performed to evaluate whether tablets are disintegrated within the acceptable time limits when put in a dissolution medium. From each brand, randomly six tablets were selected, to evaluate the disintegration time using disintegration apparatus (Agilent, QT6237QA, California, USA). The samples were placed in basket rack assembly of the disintegration apparatus. D.I. water maintained at 37±2 °C was used as a medium. Time was recorded, at which the tablets completely disintegrated. The disintegration time for each brand was compared with the maximum acceptable limits of Pharmacopoeia [20].

Analysis of sparfloxacin content

Ten (10) tablets, each containing 100 mg of sparfloxacin were accurately weighed and crushed into a uniform powder using mortar and pestle. An amount of homogenized powder (equivalent to 1 tablet weight) was weighed accurately and put into volumetric flask (50 mL capacity) containing 25 mL distilled water and mechanically shaken until completely dissolved. A 25 ml of 1N sodium hydroxide solution was added and sonicated (Isolab, Germany) for 10 min. Then, transferred 2 mL of the above solution into an another 50mL volumetric flask and made up volume with the mobile phase, mixed and filtered through membrane filter having 0.45-micron pore size. After filtration and appropriate dilution to 80 µg/mL, 20 µL sample was injected into HPLC system (Shimadzu, Tokyo, Japan) connected with UV-detector set at 292 nm. The mobile phase used for analysis was composed of 5% aqueous acetic acid, methanol and acetonitrile (70:15:15, v/v/v). The flow rate of mobile phase was set at 1.0 mL/min. The retention time was observed approximately 10.2 minutes. The content of sparfloxacin was compared with the reference

working standard solution having the same concentration of 80 µg/mL. From the peak area of SPF, the amount of drug in the sample was calculated [21].

In vitro drug release studies

In vitro drug release studies of each brand was carried out by using dissolution USP type II (paddle) apparatus (Model # QT-5825QA Agilent California, USA), run at 50 rpm. Tablets were placed in the dissolution apparatus consisted of 900 mL of sodium acetate buffer solution (pH 4.0, adjusted using 30% NaOH solution), maintained at 37 ± 0.5 °C. Sample of 5 mL was withdrawn after 30 minutes and filtered using filter paper of 0.45-micron pores size. The amount of sparfloxacin in the dosage form was analyzed by a reported HPLC method and HPLC system having UV detector set at a wavelength of 292. The amount of sparfloxacin was assessed by comparing it with the reference working standard solution having concentration of 80 µg/mL [22].

Comparison of drug release profile

To judge the release pattern of the drug from each brand as compared to reference brand, similarity factor (f_2) was applied. According to the FDA guidelines if the values of f_2 are within the range of 50 – 100%, then it indicates equivalence and if f_2 values are less than 50%, then it shows that there is no similarity between two dissolution profiles. The comparison of drug release profile was performed by using DD-solver software (Excel add in software).

Price Variation

The variation in the price of different brands was compared and evaluated in terms of quality attributes. Brand S-1 (reference) was costly as compared to other brands (S-2 to S-5) *i.e*., 678.01, 325, 400, 300 and 199 PKR per pack.

Statistical Analysis

All the tests were conducted in triplicates. The achieved data was analyzed by using SPSS and all experimental data were reported as the means ± SD. Furthermore, One-way Analysis of Variance (ANOVA) was adopted to assess the meaningful differences among the distinct brands of sparfloxacin 100 mg tablets (Table **4**).

RESULTS AND DISCUSSION

Assessment of Physicochemical Properties of Tablets

The labeling information of all brands are listed in Table **1**. All the five brands were evaluated for their physical and chemical properties as discussed in methodology. Hardness of all brands were found satisfactory and the values were found to be 9.76 to 25.61 SC as shown in Table **2**. Similar findings were also reported by Hussain *et al*. [23] and Oishi *et al*. [24]. Similarly, thickness of the all brands was found between 3.60 to 4.17 mm. Uniformity of weight test of all brands was also determined and the results were noted within the described USP specification of ± 5 %, as mentioned in Table **2** [20]. The results of friability test of all brands were less than 1 %, *i.e*., found within the limits specified in pharmacopeia [20]. Four different brands of sparfloxacin (S-2, S-3, S-4 and S-5) having variable price ranges were used as test brands, whereas, the brand S-1 was considered as reference (Table **3**) and they were found similar.

Table 2. Quality control assessment of all brands of sparfloxacin 100 mg tablets.

Brand Code	Hardness** (SC)	Thickness** (mm)	Weight Variation Test** (mg)	Friability** (%)	Disintegration Test*** (min)	Assay* (%)
S-1	9.76 ± 0.07	3.60 ± 0.50	154.85±1.599	0.30±0.06	7.50±0.19	100.0±0.75
S-2	14.01 ± 0.39	4.17 ± 0.02	431.90±1.553	0.35±0.12	12.02±0.21	99.20±0.48
S-3	7.28 ± 1.46	4.14 ± 0.01	303.55±3.252	0.60±0.10	9.86±0.27	99.0 ± 0.35
S-4	25.61 ± 0.36	3.99 ± 0.02	392.65±6.991	0.40±0.10	7.91± 0.11	97.30 ± 1.25
S-5	8.65 ± 1.50	3.75 ± 0.02	197.9 ±2.245	0.70±0.10	8.62±1.05	97.94 ± 1.05

All values are expressed as mean ± SD; *n = 10; **n = 20; ***n = 6

Disintegration test

Disintegration means how much the tablet will take time to disintegrate into its fragments. The disintegration time was recorded in the range of 7.5 – 12.02 minutes (Table **2**) showing that all brands complying acceptance limit of the USP [20]. These results indicated that S-1 took more time (12.02 min), while, S-2 took least time (7.5 min) to disintegrate.

Assay of sparfloxacin tablets

A reported HPLC method was used to carried out an assay of sparfloxacin 100 mg tablets [22]. Results of all brands were found in the range of 97.30 to 100.0% (Table **2**) and felt within the pharmacopoeial limits of 90 – 110 [20].

In vitro drug release studies

The multiple point dissolution test of each brand was performed using dissolution USP type II apparatus (paddle), run at 50 rpm. 900 mL of sodium acetate buffer solution (pH 4.0, adjusted by 30% NaOH solution), maintained at 37±0.5 °C was used as medium. Five (5) mL samples were withdrawn at an interval of 15, 30 and 45 minutes and after appropriate dilution, the amount of sparfloxacin in the sample was analyzed by using HPLC method. The amount of sparfloxacin was assessed at 292 nm by comparing it with the reference working standard solution having concentration of 80 µg/mL [22]. The results of all five brands at 30 minutes sampling, were observed in the range of 85 -90 % as shown in Table **3** and Figure **1**. No any study was reported yet, regarding the comparative brand study of sparfloxacin tablet.

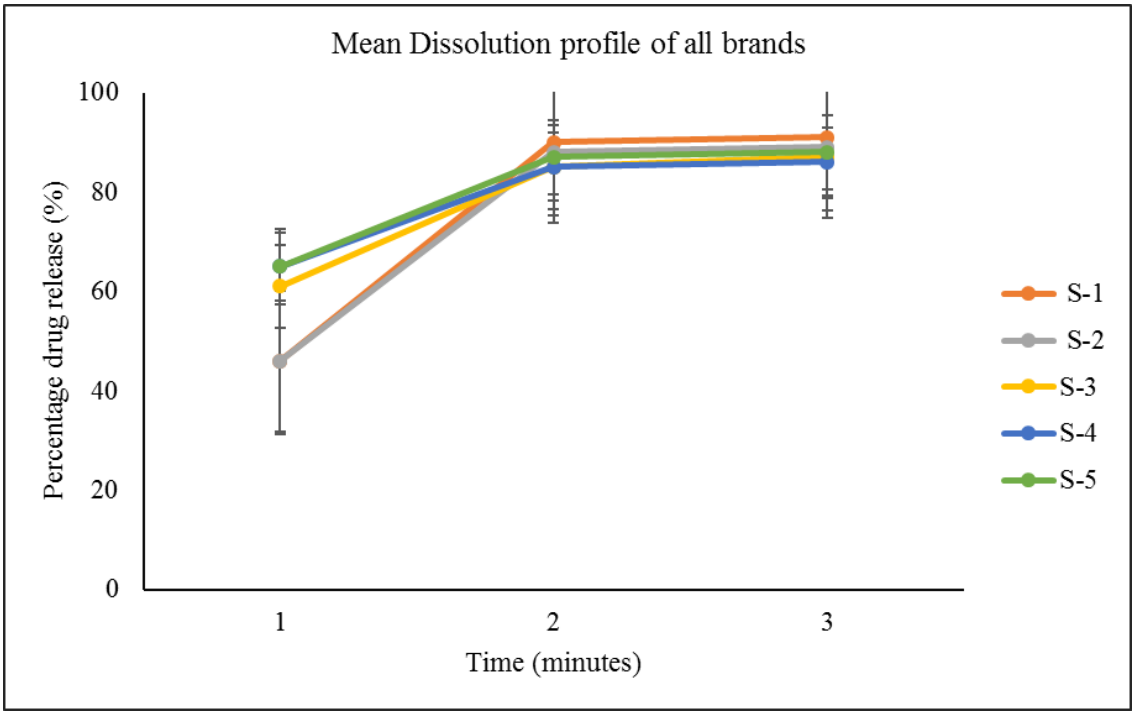

Figure 1. Mean dissolution profile of all brands.

Release profile comparison

Similarity factor (f_2) was also applied by using DD Solver (MS Excel based software) to evaluate the release pattern of the drug from each brand in comparison with reference brand (S-1). The values of similarity factor (f_2) of S-2, S-3, S-4 and S-5 were found to be 88.07, 54.27, 55.1 and 50.47, respectively, indicating that all the brands were pharmaceutically equivalent. Brand S-2 (88.07) showed more similarity in the dissolution profile than other brands when compared with S-1 (reference) brand, given in Table **3** and Figure **2**. According to the FDA guidelines, if the values of f_2 are within the range of 50 – 100%, it indicates equivalence and if the values are less than 50%, then, there is no similarity between two dissolution profiles.

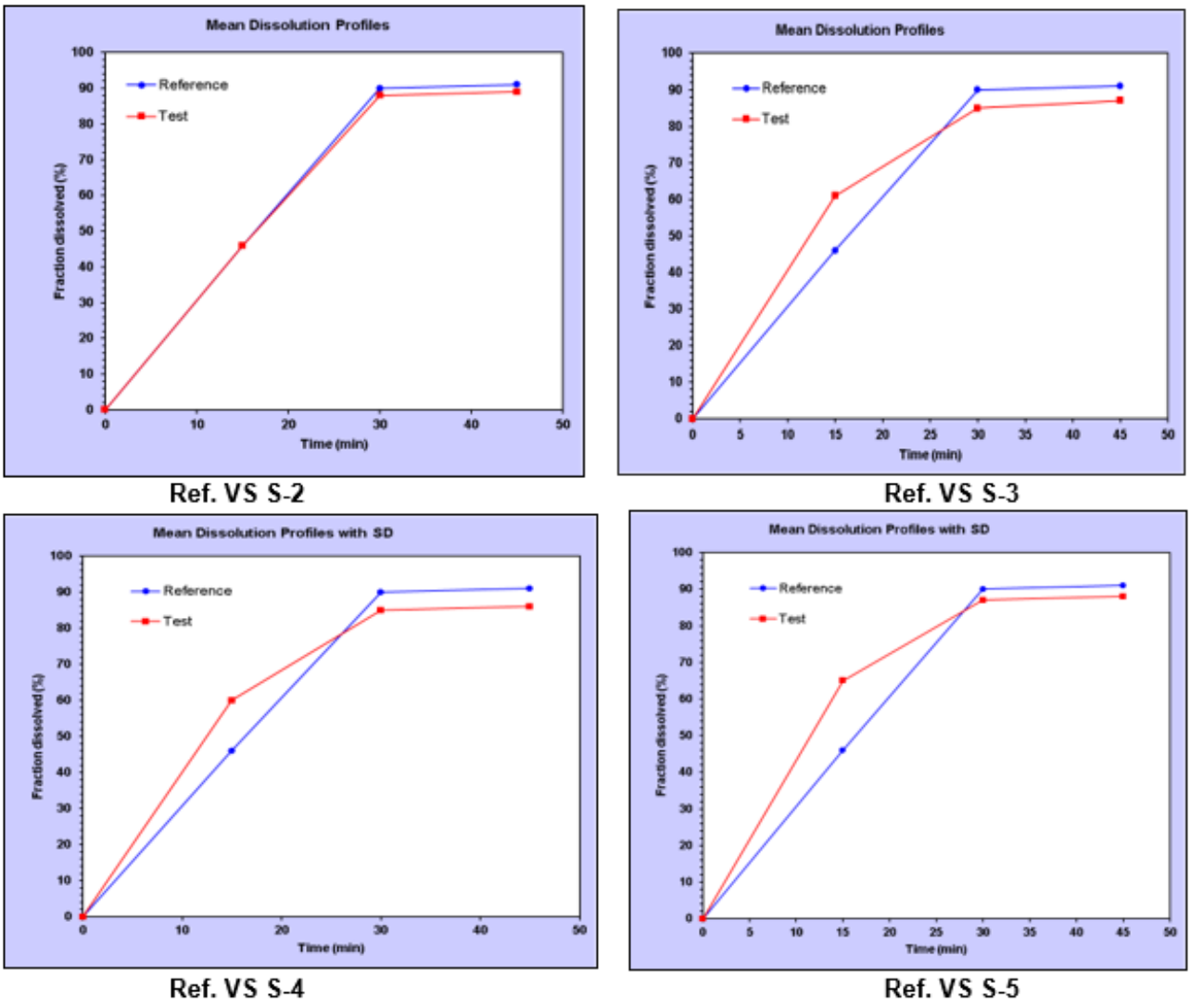

Figure 2. Comparison of dissolution profiles of all brands (S-2 to S-5) with reference brand (S-1) using DD Solver.

Table 3. Dissolution profiles of all brands of sparfloxacin 100 mg tablet at different time interval and similarity factor (f_2).

Brand Code	Dissolution rate at different time interval (Mean ± S.D*)			USP Limits	Similarity factor (f_2) values (%)
	At 15 min.	At 30 min.	At 45 min.		
S-1	46±1	90±2	91±2	Not less than 80% at 30 min	Reference (innovator)
S-2	46±3	88±2	89±2		88.07
S-3	61±2	85±5	87±3		54.27
S-4	65±4	85±3	86±3		55.1
S-5	65±3	87±2	88±1		50.47

Table 4. Statistical one-way ANOVA for the released pattern of different brands of sparfloxacin using SPSS.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	53.04353	4	13.26088	1.335858	0.284288	2.75871047
Within Groups	248.1717	25	9.926868			
Total	301.2152	29				
Total	227.7246	29				

Price Variation

Table **1** shows the price list of all brands. Brand S-1 (reference) is costly as compared to other four brands (S-2 and S-5), indicating a significant variation in the price of five brands of sparfloxacin (Rs. 199 – 678 per pack). The brand S-2 showed most similarity with the reference (S-1), not only in physicochemical studies but also in quality control analysis although its cost is approximately 50% less. Therefore, the brand S-2 can be used despite of brand S-1 as it is comparatively more expensive. Variation in cost of brands does not indicates its quality in term of effectiveness but physician, pharmacist and patients may think about it. Thus, this study may help for doctors and patients in the selection of cost effective brand having same quality.

CONCLUSION

Comparative *in vitro* study of different brands of sparfloxacin 100 mg tablet was performed. The quality of brands was evaluated by conducting different tests such as uniformity of weight, tablet breaking force, friability, disintegration time, *in vitro* drug release and sparfloxacin content tests and the results were found satisfactory. Brand S-1 and S-2 showed similar *in vitro* results but results of all other brands were also complied with the pharmacopoeial limits. It was observed that a major variation in the price was found within the same generic brands of sparfloxacin 100 mg tablets. Therefore, it can be concluded that the cost effective brand can be prescribed and used rather than expensive one.

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