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Original Research Article

Assessment of physical and dissolution characteristics of various itraconazole capsule formulations: a comparative analysis

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ABSTRACT

Background: This *in vitro* study compared physical parameters and the dissolution profile of innovator itraconazole capsule formulation, i-Tyza, and 5 other generic capsule formulations available in the Indian market.
Methods: The number of pellets and size distribution were determined using naked eye examination and sieving method, respectively. Dissolution profile of formulations was done at 15, 30, 45, and 60 minutes, using a United States Pharmacopeia type II Paddle apparatus in simulated gastric fluid (SGF, pH 1.2) without enzymes, acetate buffer (pH 4.5) with 0.5% sodium lauryl sulfate (SLS), and phosphate buffer (pH 6.8) with 0.5% SLS.
Results: All formulations had capsule size 0. Capsule fill weight (~335 to ~510 mg) and total pellet number (127 to 810) varied across formulation, with the innovator brand having the highest number of pellets. Innovator product and i-Tyza had similar fill weight (~460 mg). Pellet size distribution of the innovator product, brand 2, brand 3, and i-Tyza was relatively narrow. In SGF, except brand 1 (84% dissolved) and brand 5 (80% dissolved), all the formulations had near-complete (>85% drug dissolved) or complete dissolution (>90% drug dissolved) at 60 minutes. In acetate buffer, pH 4.5 with 0.5% SLS and phosphate buffer, pH 6.8 with 0.5% SLS, only the innovator product and i-Tyza demonstrated near-complete to complete dissolution at 60 minutes (96% and 90% dissolved).
Conclusions: Across all the itraconazole generic formulations evaluated, i-Tyza had comparable physical characteristics and dissolution profile to the innovator product. The *in vitro* dissolution profile of i-Tyza may indicate adequate *in vivo* performance.

Keywords: Itraconazole, i-Tyza, BCS class II, Capsule, Pellet, Dissolution profile, Physical characterization

INTRODUCTION

Dermatophytosis is one of the most common fungal infections, transmitted through direct skin contact with other infected humans or animals or indirect contact through communal bathing facilities, shoes, clothes, brushes, etc.[1] The global prevalence of dermatophytosis ranges between 6.5-68%.[2-6] In India, the prevalence of dermatophytosis is very high (62.28%-75.6%).[7-10] Expert consensus on The Management of Dermatophytosis recommends itraconazole as one of the preferred drugs for the systemic treatment of Indian patients with dermatophytosis.[11] Itraconazole is a potent broad-spectrum, triazole antifungal drug; it inhibits the sterol biosynthesis in the fungal cell membrane.[12,13] However, evidence suggests that orally administered itraconazole may have inconsistent bioavailability and interindividual variations.[14,15] Few reports have suggested that substitution of proprietary itraconazole formulation with the generic formulation demonstrated sub-therapeutic levels of the drug in patients, causing treatment failure and drug resistance.[16,17]

Itraconazole belongs to Biopharmaceutics classification system (BCS) class II, with low solubility (aqueous solubility: 1 ng/ml at pH 7 and 5 µg/ml at pH 1) and high permeability.[18] For BCS class II molecules, the dissolution of drug in the gastrointestinal tract could be the rate-limiting step in absorption into the systemic circulation.[19] Thus, the antifungal activity and treatment outcome of itraconazole largely depends on the formulation behavior. For enhancement of aqueous solubility, dissolution rate and bioavailability of BCS class II drugs, techniques like micronization, chemical modification, pH adjustment, solid dispersion, complexation are often employed.[20] To improve the dissolution profile of itraconazole, the innovator product is prepared by solid dispersion technology by coating inert beads or pellets (600-710 µm) with itraconazole and hydrophilic polymer (hydroxypropyl methylcellulose).[21] Pellets provide a large surface area for dissolution, thereby improving the absorption of itraconazole into the systemic circulation.[22] Hence, evaluation of pellet size and size variation is essential to determine the quality of formulations. Additionally, other parameters in the formulation such as the drug-polymer ratio, solvent composition, coating spray rate and temperature in the fluidized bed are also crucial to obtain good quality products.[21] To ensure quality and reproducibility and to minimize the number of *in vivo* studies, *in vitro* dissolution tests mimicking the *in vivo* gastrointestinal hydrodynamics are usually applied. To this effect, *in vitro* tests such as dissolution studies in multiple media are performed to predict performance of the products *in vivo*.[23,24]

In this study, we compared the physical parameters and dissolution profile of the innovator itraconazole capsule formulation and 6 other generic capsule formulations: i-Tyza (Abbott Healthcare Pvt. Ltd.), brand 1, brand 2, brand 3, brand 4, and brand 5.

METHODS

Seven brands of itraconazole capsule (100 mg) currently marketed and prescribed by health care professionals from India were included in this *in vitro* study to compare their physical characteristics and dissolution profile, across formulations. A bio-relevant dissolution test was used to identify the pellet formulation that demonstrated an optimal dissolution profile across the pH simulating the gastrointestinal tract. As the study did not involve human subjects, ethical approval was not needed to conduct this study.

Physical characterization

Physical characterization involved determination of the capsule size, fill weight, total number of pellets, number of active pellets, number of dummy pellets, and pellet size distribution. Distinction between active and dummy pellets and the count of total pellet number was done by naked eye examination and pellet size was determined by the sieving method. Sieve analysis was performed by arranging sieves in the order of their decreasing pore diameter. Pellet sizes were stratified per American Society of Testing and Material (ASTM) standards: ASTM #14 (1405 µm), ASTM #16 (1204 µm), ASTM #18 (1003 µm), ASTM #20 (850 µm), ASTM #25 (710 µm).

Dissolution profiling

Dissolution test of itraconazole capsule was performed using a United States Pharmacopeia type II (Paddle) apparatus (Labindia Analytical Instruments), at 37°C±0.5°C, 100 rpm in simulated gastric fluid (SGF, 900 ml, pH 1.2) without enzyme, acetate buffer (pH 4.5+0.5% sodium lauryl sulfate [SLS], 900 ml), and phosphate buffer (pH 6.8+0.5% SLS, 900 ml).[25,26] One itraconazole capsule was added to each of the 6 dissolution vessels and 10 ml aliquots were withdrawn at 15, 30, 45, and 60 minutes. All aliquots were filtered through 0.45 µm nylon membrane and analyzed using high-performance liquid chromatography (HPLC). For HPLC analysis, reverse phase column (Hypersil BDS C18, 150 mm × 4.6 mm, 5 µm, maintained at 25°C), mobile phase (buffer: acetonitrile of 65:35 [v/v]; flow rate 1.5 ml/min), and isocratic flow was used. During analysis, a 50 µl sample was run for 12 minutes and results were read at 225 nm. A standard itraconazole solution of 0.111 mg/ml concentration was prepared for analysis in methanol and hydrochloric acid followed by SGF without enzymes. A blank solution (dissolution medium only), standard solutions (5 replicates) and sample aliquots were injected in the HPLC system and the response of itraconazole in standard and sample solutions was measured. Percentage itraconazole release from itraconazole capsule at each time interval was calculated accordingly.

RESULTS

Physical characterization

All the formulations had a similar capsule size 0. However, capsule fill weight (~335 to ~510 mg) and the total number of pellets (127 to 810) varied across formulations. The innovator formulation and i-Tyza had almost similar fill weight (~460 mg). The innovator product also had the highest pellet number (810), followed by brand 4 (690), brand 5 (570), i-Tyza (510), and brand 1 (435). High fill weight but low pellet number were seen in brands 2 and 3 (509 mg and 127 pellets, and 508 mg and 128 pellets, respectively.

In addition to the low pellet size, the innovator formulation also had narrow pellet size distribution, with 94.27% pellets retained on sieve number 20 (850 µm). Particle size distribution of the innovator formulation, brand 2, brand 3 and i-Tyza was relatively narrow (Table 1). All the formulations had only active pellets and none of the selected formulations included dummy pellets.

Table 1: Physical parameters of different itraconazole formulations.

Products	Innovator	Brand 1	Brand 2	Brand 3	Brand 4	Brand 5	i-Tyza
Capsule size	**Size 0**	**Size 0**	**Size 0**	**Size 0**	**Size 0**	**Size 0**	**Size 0**
Fill weight (mg)	~460	~335	~509	~508	~510	~485	~460
Total no. of pellets	810	435	127	128	690	570	510
No. of active pellets	810	435	127	128	690	570	510
No. of dummy pellets	-	-	-	-	-	-	-
Pellet size distribution	**% retained**						
ASTM # 14 (1405µm)	0.00	0.00	98.17	96.82	0.00	0.00	0.00
ASTM # 16 (1204µm)	0.39	0.00	1.83	3.18	0.00	0.92	1.09
ASTM # 18 (1003µm)	2.08	37.01	-	-	60.25	78.58	87.90
ASTM # 20 (850µm)	94.27	46.27	-	-	35.32	19.51	10.53
ASTM # 25 (710µm)	3.27	16.72	-	-	4.43	0.99	0.47

ASTM: American Society for Testing and Materials; Based on visual observation, there were no dummy pellets in any formulation.

Table 2 (A): Dissolution profile of different itraconazole formulations in simulated gastric fluid, pH 1.2 without enzymes.

Products	Mean % drug release						
Time (minutes)	**Innovator**	**Brand 1**	**Brand 2**	**Brand 3**	**Brand 4**	**Brand 5**	**i-Tyza**
15	39	5	37	23	60	1	39
30	63	23	79	76	96	18	81
45	79	60	98	99	102	59	97
60	89	84	100	102	104	80	102

Mean values are obtained from 6 units. For Brand 1, values were obtained from 5 units.

Table 2 (B): Dissolution profile of different itraconazole formulations in acetate buffer pH 4.5 with 0.5% sodium lauryl sulfate.

Products	Mean % drug release						
Time (minutes)	**Innovator**	**Brand 1**	**Brand 2**	**Brand 3**	**Brand 4**	**Brand 5**	**i-Tyza**
15	18	11	5	6	5	3	22
30	49	71	33	35	18	35	64
45	75	82	52	58	33	51	92
60	88	86	64	69	43	77	98

Mean values are obtained from 6 units.

Table 2 (C): Dissolution profile of different itraconazole formulations in phosphate buffer pH 6.8 with 0.5% sodium lauryl sulfate.

Products	Mean % drug release						
Time (minutes)	**Innovator**	**Brand 1**	**Brand 2**	**Brand 3**	**Brand 4**	**Brand 5**	**i-Tyza**
15	21	2	4	2	4	8	16
30	56	17	17	10	16	20	46
45	83	35	30	19	30	50	81
60	96	46	37	26	43	78	90

Mean values are obtained from 6 units.

Dissolution profiling

In the SGF medium, all the other formulations had near-complete (>85% drug dissolved) or complete dissolution (>90% drug dissolved) at 60 minutes, except for brand 1 (percent dissolved: 84%) and brand 5 (percent dissolved: 80%). In acetate buffer medium (pH 4.5 with 0.5% SLS), only the innovator product (percent dissolved: 88%) and i-Tyza (percent dissolved: 98%) had near-complete or complete dissolution at 60 minutes. Similarly, in phosphate buffer medium (pH 6.8 with 0.5% SLS), only the innovator product (percent dissolved: 96%) and i-Tyza (percent dissolved: 90%) achieved complete dissolution at 60 minutes (Table 2, Figure 1).

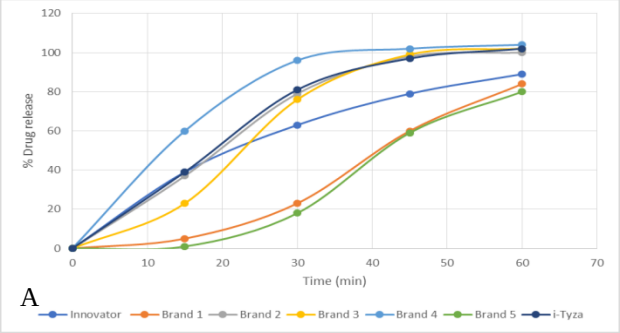

Figure 1 (A): Comparative dissolution profile of different itraconazole formulations in simulated gastric fluid, pH 1.2 without enzymes.

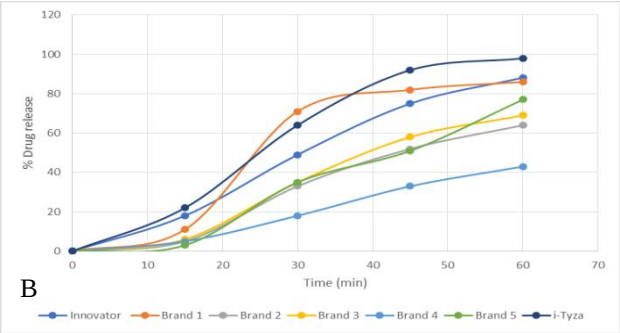

Figure 1 (B): Comparative dissolution profile of different itraconazole formulations in acetate buffer with 0.5% SLS (pH 4.5).

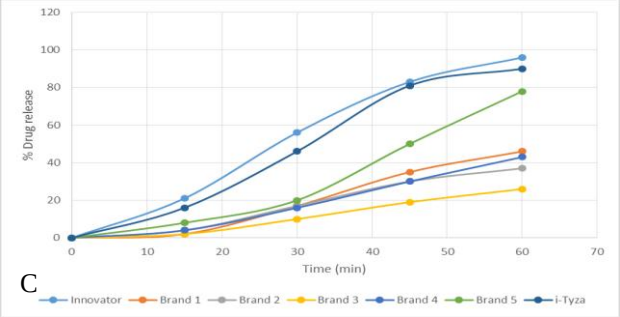

Figure 1 (C): Comparative dissolution profile of different itraconazole formulations in phosphate buffer with 0.5% SLS (pH 6.8).

DISCUSSION

This study compared the physical parameters and dissolution profile of various itraconazole capsule formulations routinely prescribed by health care professionals for treating dermatophytosis. This is essential as poor bioavailability may have an impact on the clinical outcomes. We found that the innovator product had a high pellet number, and low fill weight and pellet size variation. These physical characteristics were comparable with 2 generic formulations, i-Tyza and brand 5. However, compared with brand 5, dissolution profiles of i-Tyza were better across all the dissolution media. Thus, our results suggest that compared with other itraconazole formulations, the physical parameters and dissolution profile of i-Tyza have a greater similarity with the corresponding parameters of the innovator product.

Itraconazole is a preferred, orally administered drug for the treatment of dermatophytosis.[11] However, its bioavailability and, in turn, efficacy may vary with formulation change because of its physicochemical properties (low solubility) and formulation-dependent factors such as the drug-polymer ratio, solvent composition, pellet size.[16,17,21] Hence, an itraconazole formulation (pellets) with an optimal dissolution profile is essential for adequate treatment response.[21,22]

In this study, the innovator product had the smallest pellet size, with majority of pellets falling in the range of 850 µm to 1003 µm. The pellet size of generic formulations, i-Tyza, brand 5, and brand 4 was closer to that of the innovator product with majority of the pellets in the size range of 850-1204 µm. However, among the generic formulations, least pellet size variation was observed for i-Tyza. In another morphometric study that compared the innovator product with 21 other generic formulations, similar results were observed for the innovator product (average pellet size 969 µm and pellet size range 893-1184 µm).[27] Pellet size variability is a parameter that indicates the quality of formulation.[28] High variability is indicative of poor quality formulation and, in turn, variable dissolution profile. Drugs with less pellet size variation may have less erratic gastrointestinal absorption profile.[27] Hence, poor physical parameters may cause erratic absorption and adversely affect bioavailability.

In the present study, pellet number was highest for the innovator product, followed by brand 4, brand 5, and i-Tyza. A similar result for the pellet number of the innovator product was observed by Sardana et al (2018).[27] The authors also reported a large variation in pellet number and average pellet size among different brands, however the authors did not perform the dissolution studies. Dissolution of itraconazole from drug product is critical for clinical performance and it depends not only on pellet number but also on pellet size and manufacturing technology.[29] Despite having differences in pellet number, i-Tyza demonstrates comparable dissolution with innovator product. This was made possible by carefully selecting the drug-polymer ratio and also precisely controlled and robust manufacturing process.

The United States Food and Drug Administration guidelines for dissolution testing of immediate-release solid oral dosage forms recommend that drugs belonging to BCS class I or III and having high solubility, 85% dissolution in SGF in 15 minutes ensures that bioavailability is not dissolution dependent. However, for BCS class II drugs, such as itraconazole, dissolution is a rate-limiting step for absorption; hence, dissolution

profile in multiple media is recommended to establish an *in vitro-in vivo* correlation.[24] In this study, we assessed the dissolution profile of itraconazole formulations in SGF without enzymes, acetate buffer, pH 4.5 with 0.5% SLS, and phosphate buffer, pH 6.8 with 0.5% SLS, which mimic the pH conditions in the stomach and intestines. In SGF without enzymes, the innovator product, i-Tyza, brand 2, brand 3, and brand 4 had near-complete dissolution at 60 minutes. In the acetate buffer, pH 4.5, only i-Tyza (percent dissolved: 98%) and the innovator product (percent dissolved: 88%) had a near-complete dissolution at 60 minutes. In phosphate buffer, pH 6.8, only i-Tyza showed complete dissolution similar to that of the innovator product. Biorelevant *in vitro* dissolution is a useful technique for qualitative forecasting of the *in-vivo* behavior of a formulation. Considering the site of absorption of itraconazole, phosphate buffer, pH 6.8 with 0.5% SLS can be considered as a biorelevant media. The dissolution profile of i-Tyza was similar to that of the innovator product in phosphate buffer, pH 6.8 with 0.5% SLS with 96% and 90% dissolution at 60 minutes, respectively, giving a high degree of assurance of similar *in vivo* performance.

The study had few limitations. We assessed the samples from a single batch, hence inter-batch variability of formulations could not be ruled out. Furthermore, statistical analyses were not done to compare the physical profile of the formulations; hence determination of statistical significance of the comparisons across formulations was not possible.

CONCLUSION

A novel formulation of itraconazole, i-Tyza, had comparable quality to that of the innovator product. The physical parameters and dissolution profiles of i-Tyza were relatively favourable compared with those of other generic formulations available in the Indian market.

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