Short Communication

Pharmaceutical quality evaluation of marketed vildagliptin tablets in Bangladesh based on the United States Pharmacopeia specifications

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Abstract

Continuous monitoring of pharmaceutical products is vital because it matters to human health. Here we aimed to assess the quality parameters of commercially available vildagliptin tablets in Bangladesh. We tested the tablets for the content uniformity, hardness, friability, disintegration, dissolution, and potency. Then, we fitted the dissolution data with kinetic models to investigate the release pattern of the studied brands. Moreover, we applied a mathematical model-independent approach to compare the dissolution profiles of the brands. The interchangeability was determined using difference and similarity factors. Weight variation, friability, and hardness were between 150.35±1.26 to 230.8±1.98 mg, 0 to 0.88%, and 47.3±5.09 to 108.1±1.92 N, respectively. All tablets disintegrated within 0.54±2.85 to 7.69±2.14 min in distilled water. The potency of tablets in 0.1 N HCl and PBS (pH 6.8) were between 97.67±2.58 to 105±0.95% and 99±4.63 to 105±1.65%, respectively. The drug release (%) in 0.1 N HCl and phosphate-buffered saline (PBS) (pH 6.8) after 60 min were between 99.37±1.80 to 111.09±0.64% and 96.59±3.52 to 109.57±0.53%, respectively. All the brands complied with the United States Pharmacopeia (USP) specification for physicochemical properties. Also, we observed the drug release patterns of vildagliptin tablets matched with different kinetic models. We found only one substitutable brand with the standard product regardless of the dissolution medium. In-vitro chemical equivalence is not always consistent with bioequivalence. Therefore, continuous evaluation of marketed products is essential to ensure the desired quality.

Keywords: Vildagliptin, pharmaceutical quality, physicochemical properties, dissolution profile, pharmaceutical market

Introduction

*T*he oral antidiabetic drug vildagliptin was first introduced in the market by Novartis in 2007 [1]. According to the Directorate General of Drug Administration (DGDA) of Bangladesh, more than 20 companies are locally manufacturing vildagliptin tablets [2]. A regular quality assessment of marketed pharmaceutical products is essential to ensure desired pharmacological benefits and minimize drug use risks [3]. Adulterated, falsified, and sub-standard medicines cause severe health problems in low- and middle-income countries. It is happening only

because of the lack of pharmacovigilance activities and proper monitoring of drug regulatory authorities [4]. These low-quality medicines increase the healthcare cost and sufferings of patients [5-7]. Spreading this poor-quality medicine having little or no therapeutic effects put the population at the risk of drug resistance, posing a threat to overall treatment effectiveness, and undermining people's trust in the health care system and health care professionals [8-12]. Post-marketing evaluation of quality parameters is vital to monitor the safety, quality, therapeutic efficacy of drugs, and patient compliance [13]. The high levels of substandard or counterfeit pharmaceutical products are present in poor and developing countries [14]. The present study aimed to evaluate the quality parameters of locally manufactured vildagliptin 50 mg tablets available in Bangladesh.

Methods

Drugs and chemicals
We randomly collected nine brands of vildagliptin 50 mg tablet from various local pharmacies in Dhaka, Bangladesh. We meticulously examined the purchased products for physical appearance, name of the manufacturer, batch number, date of manufacturing, date expiry, manufacturing license number, and price. We marked the purchased samples as R1, reference brand (originator brand); the remaining generic brands as G1, G2, G3, G4, G5, G6, G7, and G8. All the chemicals and reagents used in this study were analytical grade and purchased from globally reputed sources. We obtained the reference standard of vildagliptin from ACI Limited, Dhaka, Bangladesh.

Quality control tests and calculations
We performed the weight variation test by taking the individual weight of arbitrarily selected twenty tablets from each brand. We calculated the hardness of a specific tablet brand after determining the average crushing strength. Twenty tablets of each of the brands were weighed and exposed to vibration using a friabilator at 25 rpm for 4 min. After completing 100 revolutions, the tablets gently were dedusted and weighted again to compare with their initial weights. We calculated the percentage of friability for each of the brands from the weight differences.

We conducted the disintegration test using six tablets from each of the nine brands in distilled water media. To determine the disintegration time (DT), six tablets from each of the nine brands were randomly picked and placed them in each vessel at 37±0.5°C. We recorded the DT when all the particles of the tablet moved through the mesh screen.

Twenty tablets were picked randomly from each brand and pulverized into homogenized powder. Fifty-milligram vildagliptin equivalent powder was taken in a flask and dissolved in 0.1N hydrochloric acid (HCl) medium. We dissolved the same amount of powder in phosphate-buffered saline (PBS) at pH 6.8. We performed sonication to dissolve the powder homogenously. The solution was filtered using a filter paper with a pore size of 0.45 µm. Then, 1 ml of each filtrate was taken in two different test tubes and diluted to 10 ml by using the respective medium. The absorbance of the solution against the reagent blank at 218 nm was measured using an UV-VIS spectrophotometer (Shimadzu, Kyoto, Japan). The absorbance value was inputted in the linear regression equations and the concentration was measured to calculate the potency of tablets.

The dissolution test of six vildagliptin tablets from each brand was conducted using the dissolution apparatus USP II (Paddle apparatus) (Electrolab, Mumbai, India) at 50 rpm. A total of 900 mL 0.1N HCl was used as a dissolution medium at 37±0.5°C. The 10 mL of the dissolution sample were withdrawn at 0, 10, 20, 30, 40, 50, and 60 min and replaced with an equal fresh medium to sustain sink condition. Samples were filtered and assayed by an UV-VIS spectrophotometer (Shimadzu, Kyoto, Japan). spectrophotometer at 218 nm. We determined the concentration of each solution using the calibration curve obtained from the standard vildagliptin. We repeated the whole procedure using PBS (pH=6.8) as a dissolution medium.

Results

All the brand of vildagliptin tablets used in this evaluation study was within the shelf life. The labeled shelf life of all tablets was two years from the date of the manufacturing. In vitro tests were performed to judge the quality parameters of collected tablets. There were no deviations found in the physical appearances of all the samples from nine different brands. The label information and comparative parameters of the assessed tablets are presented in **Table 1**.

We used the United States Pharmacopeia (USP) specifications as reference to evaluate the pharmaceutical quality of the vildagliptin. The USP specifications are weight variation, not more than (NMT) ±5% to±7.5%; hardness, 40-100; friability, 1%; disintegration time, 5-30 min; potency, 95-105%. The weight variation (mean±%RSD) of R1 was 174.85±1.26 mg, the range for the mean weight of the nine brands were 150.35±1.26 to 230.8±1.98 mg. For weight variation, all the brands complied with the USP specification. The generic brand G7 demonstrated the highest deviation (3.11%) from the official specification. Brand G3 showed the lowest deflection (0.68%). The mean hardness of R1 was 77.8±3.12 N, ranged from 47.3±5.09 to 108.1±1.92 N for G1-G8. We observed two brands (G3 and G4) that failed to comply with the USP specification for the hardness test. Weight loss ranged from 0-0.88% for all brands during the friability test. Two brands (G6 and G7) showed zero weight loss. We observed the maximum weight loss in the generic brand G8 (0.88%).

The mean DT for R1 was 1.62±2.81 min conducted in the distilled water medium, ranged from 0.54±2.85 to 7.69±2.14 min for G1-G8. The lowest and the highest DT produced by brand G2 and G7, respectively. In the current experiment, all the nine brands all met the official specification for DT. We presented the drug release pattern in 0.1N HCl and PBS (pH 6.8) media in **Figure 1**. Along with the reference brand R1, all the generic products (G1-G8) showed more than 80% release within their first 60 min in both dissolution media. Two genetic brands (G1 and G3) showed the smallest deviation from the official specified limit. The potency of all the brands was 97.67-105% and 99-105% in 0.1N HCl and PBS at pH 6.8, respectively.
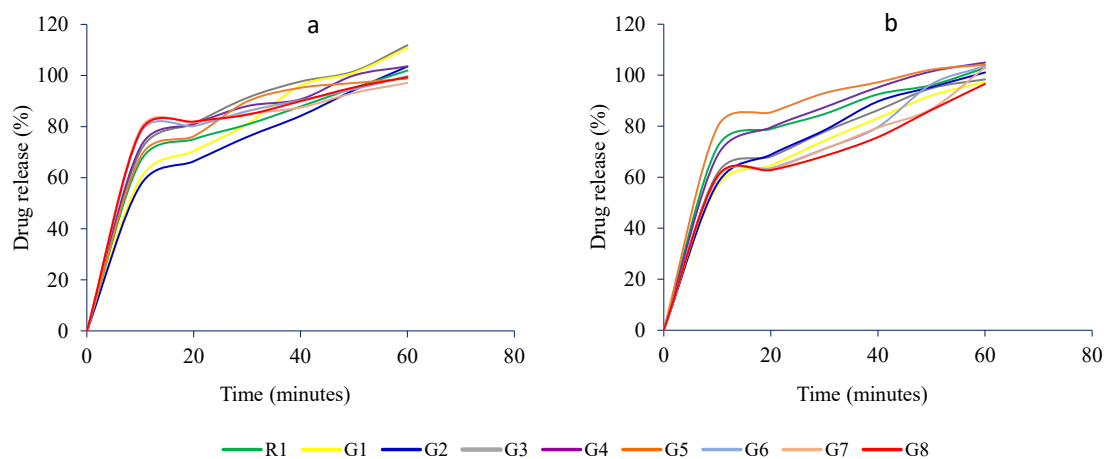

Figure 1. The dissolution profile of vildagliptin tablet brands available in the Bangladesh market in 0.1N hydrochloric acid (HCl) (a) and phosphate-buffered saline (PBS) at pH 6.8 (b). R1, reference brand; G1-G8, generic brands.

We applied different kinetic models to determine R^2 values using various parameters. Generic brands G3 and G5 fitted with the first-order kinetic model; Kopcha kinetic model was the best fit to generic brand G1 and G7; the Korsmeyer-Peppas model was the best fit to generic brand G2, G4, G6, G8, and reference brand R1 in 0.1N HCl medium. Similarly, Kopcha kinetic model was the best fit for generic brand G3, G6, G7, and G8; the Korsmeyer-Peppas model was the best fit for generic brand G1, G2, G4, G5, and reference brand R1 in PBS at pH 6.8.

Table 1. Label information and comparison of vildagliptin 50 mg tablets available in Bangladesh

Characteristics	Brand of vildagliptin								
	Reference brand	Generic 1	Generic 2	Generic 3	Generic 4	Generic 5	Generic 6	Generic 7	Generic 8
Manufacturing date	Feb 2017	Dec 2016	Jul 2017	Dec 2016	Jul 2017	May 2017	Apr 2017	Dec 2017	Oct 2016
Expiry date	Jan 2019	Dec 2018	Jul 2019	Dec 2018	Jul 2019	May 2019	Mar 2019	Dec 2020	Sep 2018
Weight variation (mean±% RSD) [a]	174.85±1.26	180.4±0.87	160±0.76	199.65±0.55	224.25±0.99	150.35±1.26	206.95±1.17	230.8±1.98	184.25±1.29
Hardness (N) [b]	77.8±3.12	67±2.96	95.7±1.48	104.1±5.25	108.1±1.92	47.3±5.09	56.4±3.26	77.4±4.36	66.7±5.10
Friability (%) [c]	0.49	0.70	0.35	0.21	0.51	0.58	0.00	0.00	0.88
Disintegration time (min) [d]	1.62±2.81	5.34±0.37	0.54±2.85	4.12±0.61	1.87±2.49	2.20±1.84	1.95±1.56	7.69±2.14	1.14±1.34
Potency (%) [e]									
In 0.1N HCl	104.67±0.55	100.67±1.52	104.67±1.46	105±0.95	102±0.98	102.3±0.56	103±1.68	104.67±1.10	97.67±2.58
In PBS at pH 6.8	104.3±2.93	99±4.63	103±0.97	101±0.99	103.33±1.48	101±0.99	105±1.65	103±2.91	101±1.71
Drug release pattern (R^2)									
Zero order kinetic model (0.1N HCl)	0.719	0.831	0.822	0.819	0.669	0.672	0.579	0.555	0.586
Zero order kinetic model (PBS at pH 6.8)	0.643	0.801	0.783	0.763	0.714	0.607	0.883	0.868	0.848
First order kinetic model (0.1N HCl)	0.919	0.947	0.898	0.967	0.923	0.988	0.817	0.882	0.871
First order kinetic model (PBS at pH 6.8)	0.967	0.944	0.970	0.943	0.963	0.960	0.871	0.772	0.863
Kopcha kinetic model (0.1N HCl)	0.935	0.966	0.332	0.945	0.929	0.940	0.903	0.895	0.901
Kopcha kinetic model (PBS at pH 6.8)	0.924	0.955	0.964	0.993	0.945	0.915	0.932	0.928	0.919
Korsmeyer-Peppas kinetic model (0.1N HCl)	0.972	0.963	0.973	0.953	0.977	0.967	0.928	0.865	0.912
Korsmeyer-Peppas kinetic model (PBS at pH 6.8)	0.982	0.972	0.990	0.967	0.984	0.966	0.884	0.878	0.843
Difference factor (f_1)									
In 0.1N HCl medium	-	-2.36	5.09	-9.24	-5.49	-3.54	-4.14	-3.20	-4.37
In PBS at pH 6.8	-	11.20	6.85	7.59	-1.87	-6.53	9.99	12.08	14.61
Similarity factor (f_2)									
In 0.1N HCl medium	-	59.23	61.48	54.23	64.56	64.41	62.35	59.38	61.04
In PBS at pH 6.8	-	48.51	55.39	56.21	74.19	60.15	47.78	46.29	43.54

DT: disintegration time; HCl: hydrochloric acid; PBS: phosphate buffer solution; RSD: relative standard deviation' R2: regression coefficient.
USP specifications: weight variation, NMT±5% to±7.5%; hardness, 40-100; friability, 1%; disintegration time, 5-30 min; potency, 95-105%.
a: 20-time replication for each brand
b: 10-time replication for each brand
c: 20-time replication for each brand
d: 6-time replication for each brand
e: 6-time replication for each brand

Discussion

We evaluated the pharmaceutical quality parameters of eight genetic brands of vildagliptin 50 mg tablet and a reference brand available in Bangladesh. According to the present study results, all the brands passed in-vitro quality tests as per USP specification [15,16]. The average weight of the investigated tablets was between 130 mg to 324 mg. According to USP specification, not more than two tablets should deviate from the average weight by more than 7.5%; none should depart by 15% of the average weight [16-18]. The improper granulation and flow properties cause weight variation of tablet dosage form [19,20]. We observed the uniformity for Active Pharmaceutical Ingredient (API) distribution in all the analyzed vildagliptin tablet brands for the desired therapeutic effect. Hardness is a good indicator of the physical strength of a tablet that influences the disintegration process. Therefore, optimum tablet hardness is required to resist the powdering and friability of tablets [21]. For oral tablets, hardness generally ranged from 39.228 N to 98.07 N [22]. The present study observed two brands that showed deviation from this specification. But the DT of those two brands were within the standard specification. Since the hardness test is an unofficial test, and later their DT was found satisfactory, the investigated brands of vildagliptin tablets were supposed to have good quality [21-23]. Friability test is employed to determine the strength of tablets to resist mechanical shocks during production and transportation. Friability test ensures the good mechanical robustness of the tablets [24]. The compendium specification for friability is not more than 1% [15,16]. All nine brands complied with the specification. The percentage of friability in all formulations decreases where the hardness is high. The reason behind this is the high compression force during the granulation procedure [25].

The DT test determines whether tablets disintegrate within the prescribed time under the experimental condition [26]. DT plays a crucial role in the dissolution. Before absorption, the active ingredients of the tablet must go into a solution first. When the tablet breaks down into smaller particles or granules, this event is known as disintegration [27]. The optimum disintegration and dissolution profiles ensure the required bioavailability of tablet dosage form [28]. Therefore, the type and extent of disintegrating agents present in the tablet mainly affect the dissolution profile [29]. USP specifies that uncoated/film-coated tablets should disintegrate within 30 minutes [19]. According to the United States Food and Drug Administration (FDA), a minimum of 85% of an active drug should release into the medium within the first 60 minutes from their solid dosage form [30]. All brands of vildagliptin complied with this specification except generic brand G1 and G3. These two brands showed a slight deviation from the USP specification in 0.1N HCl medium [16].

The assay test indicates the presence, absence, and quantity of API in the dosage forms [31]. The official specification for the assay test is unavailable for vildagliptin as it is an INN drug. The acceptable potency range is 90-110% of the labeled amount for a highly potent drug with a minimum dose [32]. As the present study assessed the high-dose vildagliptin tablets (50 mg), the percent potency was supposed to be within 95%–105% [16]. All the examined brands complied with this specification. We performed analysis of variance (Anova) to compare the drug release pattern among different vildagliptin brands. The results indicated that there were significant differences in the release pattern among the brands in both media ($p<0.05$) (**Table 1**). The difference factor (f_1) and the similarity factor (f_2) were applied to compare the dissolution profiles among the brands [33]. To establish similarity and bioequivalence between two dissolution profiles, f_1 should be between 0 and 15; f_2 should be between 50 and 100 [29]. We found generic brand G2 having an f_2 value greater than 50 and an f_1 value of less than 15 in both media. We observed the generic brand G2 was interchangeable with the standard reference brand R1.

The present study has some limitations. We evaluated a few brands to assess the quality of available vildagliptin tablets. Therefore, the results of this study do not necessarily apply to all the available vildagliptin brands in Bangladesh. Moreover, we collected samples from Dhaka only; the distribution of quality vildagliptin brands in other areas might be different.

Conclusion

Our data suggest no significant difference observed in quality parameters for the investigated vildagliptin brands available in Bangladesh. All nine vildagliptin brands demonstrated overall quality, sufficient dissolution rate, and adequate potency. The bioequivalence of a drug is not always determined by in-vitro chemical equivalence; therefore, continuous evaluations of the marketed products are required to ensure the quality of the drugs and prevent counterfeit or substandard products.

Ethics approval

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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Underlying data

The data reporting in this study will be available from the corresponding author upon reasonable request.

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