

Original Research Article**PHARMACEUTICAL QUALITY OF GENERIC SITAGLIPTIN TABLETS COMPARED WITH JANUVIA®****Nebal Betari, Samer Haider ***

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ABSTRACT

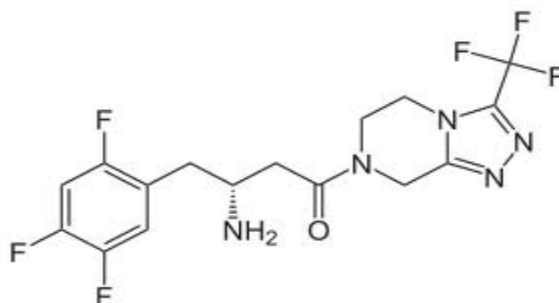
Sitagliptin is relatively new hypoglycemic agent. Several generic products are available in the Middle East. However, their pharmaceutical quality which affect safety and efficacy is unknown. Hence, prescribing of some generic products may lead to serious consequences. Januvia tablets were used as reference to determine the quality of five commercial brands of Sitagliptin selected from different Middle East commercial brands. Weight variations, content uniformity, friability, disintegration and dissolution profile were compared. All tested generics of Sitagliptin were complied with the specific requirements for quality control tests of the United State Pharmacopeia 31, whereas the result of two product were not similar to Januvia in dissolution profile, no significant differences in the results of weight variations, content uniformity, friability, disintegration. Differences in dissolution profile are due to the differences in formulations so It can be assumed that most of Sitagliptin generic products are as therapeutically effective as Januvia.

Key Words: Sitagliptin, Januvia, Pharmaceutical quality, f_1 , f_2 factors, dissolution profile.

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Running Title: Quality of Commercial Sitagliptin compared with Januvia®**INTRODUCTION**

Sitagliptin is (3R) -3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5h- [1,2,4] triazolo [3,4-c] pyrazin-7-yl]-4-(2,4,5-trifluorophenyl) butan-1-one, the empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32 [3-7] Fig.1,

**Figure 1:** Chemical structure of Sitagliptin.

Sitagliptin was approved in 2006 [1-2], as an oral hypoglycemic agent that blocks Dipeptidylpeptidase-4 (DPP-4) activity. Sitagliptin increased incretin levels (GLP-1 and GIP) which inhibit glucagon release, in turn decreases blood glucose, but more significantly increases insulin secretion [3-5]. This product was developed and marketed by [Merck](http://www.merck.com) under the trade name Januvia.

Several generic products containing Sitagliptin have been registered in the world as well as in the Middle East by several pharmaceutical companies and are present in the Middle East market.

Quality control of drugs is an important subject and plays a main role in the examination of the finished product. The supply of essential drugs of good quality was identified as one of the prerequisites for the delivery of health care [8]. It is important, from a quality control point of view, to perform a comparative analytical evaluation between trademarked and generic formulations containing Sitagliptin to assure the quality of generics [7,9-11]. Weight variation, content uniformity, hardness, friability and dissolution tests are the most important tests to be administered. Furthermore, difference (f1) and similarity (f2) tests can also apply to evaluate the tablets differences and similarities of their dissolution profiles.

MATERIALS AND METHODS

Samples: Five commercially samples containing 100 mg tablets of Sitagliptin from different companies were purchased from the Middle East market for the study and were coded as 1-5 and Januvia tablet containing Sitagliptin (100mg) was also used as the reference product. All products tested were stored within specified conditions and were within their expiry date.

Apparatus/Instruments: Dissolution test apparatus USP type I apparatus (basket) LID- 6, tablet dissolution tester – Vanguard pharmaceutical machinery, inc. USA, UV visible spectrophotometer: Mecasys, Optizen322ou. Hardness tester LIH-1, 6 tablet hardness tester – Vanguard pharmaceutical machinery, inc. USA. Disintegration test apparatus LIJ-1 tablet disintegration tester –Vanguard pharmaceutical machinery, inc. USA. Friability test apparatus LIC-2 tablet friability tester – Vanguard pharmaceutical machinery, inc. USA. PM-300 Lap Balance 0.001 g.

Analytical method for the assay of Sitagliptin: To determine the standard calibration curve of Sitagliptin, a stock solution of 100 µg/mL was prepared in distilled water. Then dilutions were made to prepare a series of solutions containing Sitagliptin in different concentrations, solutions containing 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 µg/mL of Sitagliptin (table 1).

Table 1: Absorbance versus corresponding concentrations using UV method for the determination of Sitagliptin using DDQ.

	1	2	3	4	5	6	7	8	9	10
Conc. µg/mL	10	20	30	40	50	60	70	80	90	100
absorbance	0.061	0.0582	0.104	1.139	0.174	0.208	0.244	0.278	0.313	0.328

The absorbance of these solutions was measured by a validated and stability indicated UV spectrophotometric method (Parag, Pathade et. al.) at 267 nm on UV-Visible spectrophotometer against distilled water as blank [12]. The standard curve was performed and the linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations [13] fig.2.

LOD and LOQ determination: The limit of detection (LOD) and the limit of quantitation (LOQ) were determined by using the following equations:

$$\text{LOD} = 3 \text{ SD/m}$$

$$\text{LOQ} = 10 \text{ SD/m}$$

Where SD is the standard deviation of the absorbance values (n=6) of the second smallest concentration = 0.0001

m is the slope of the calibration curve = 0.003

LOD = 0.1 µg/mL

LOQ = 0.3 µg/mL

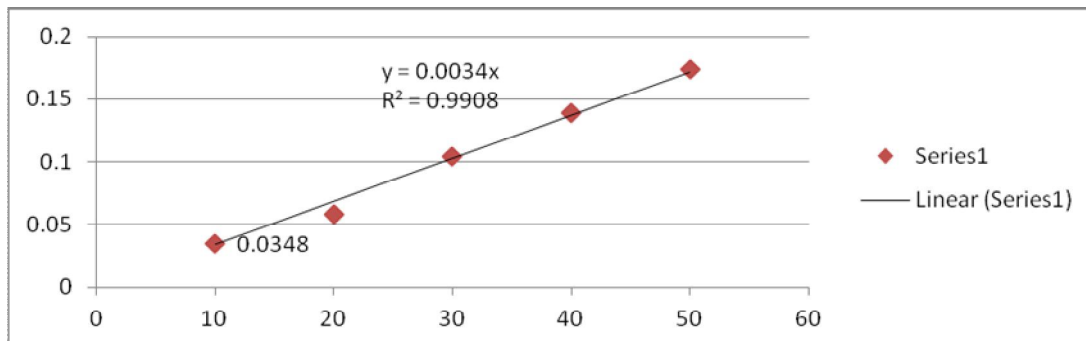


Figure 2: Plotting graph of absorbance versus corresponding concentrations.

Evaluated physical characteristics for quality control studies:

Weight variation: Each tablet (n=20) belonging to each brand was weighed with a sensitive electronic balance [14].

Hardness test: This test was applied on 10 tablets for each brand [14].

Friability test: 20 tablets from each brand were weighed and put into the tablet friability tester. Tablets were rotated at 25 rpm, then, the friability percentage was calculated for each brand [14].

Content uniformity test: 20 tablets from each brand were weighed and powdered then 50 mg from each brand was accurately weighted and determined according to USP 31[14]. A standard solution was prepared by dissolving pure Sitagliptin in distilled water and a sample solution was also prepared by dissolving the powder of Sitagliptin tablets from each batch in distilled water. The absorbance of the prepared solutions were measured at 267 nm on UV-Visible spectrophotometer against distilled water as blank and calculated by using the equation for the calibration curve. This Procedure was three times repeated for each brand and the average was taken.

Dissolution studies: The dissolution rate studies on conventional Sitagliptin tablets were carried out according to the FDA, the protocol for the dissolution study of Sitagliptin tablets was: Apparatus I (Basket), speed: 100 rpm, No. of tablets: 6 units, dissolution media: water (900 ml). Sampling interval: 5, 10, 15, 20 and 30 min, Sampling volume: 5 ml, Replenishing fluid: Water. Temperature: 37°C ± 0.5°C, analytical Method: UV Spectrophotometry (λ_{max} =267 nm) [15].

Comparison of the dissolution profiles: In this study, as model-independent approaches, two fit factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These fit factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product. The fit factors are denoted difference (f1) and similarity (f2) factors are defined by the following equations[16]:

$$f_1 = \{[\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t]\} \cdot 100$$

$$f_2 = 50 \cdot \log \{[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{0.5} \cdot 100\}$$

n = number of time point

R_t = dissolution value of the reference batch at time t

T_t = dissolution value of the test batch at time t

RESULTS

The results obtained from the performed tests were given in Table 2, Sitagliptin tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of active drug. Content uniformity test results showed that all conventional Sitagliptin tablets fit this criteria (Table 2).

Table 2: The hardness, disintegration time and drug content of sitagliptin tablets.

Code	Hardness ^a , and (Kg/cm ²)	Disintegration time ^b (Min)	Drug content Percentage ^c (%)
Januvia	05± 0.81	10.00-10.30	100.12±%
Product 1	07.62± 0.65	09.50 -11.00	98.77±%
Product 2	7.12 ± 0.75	11.30-12.00	98.75±%
Product 3	05.12± 0.91	07.75 -8.00	95.52±%
Product 4	06.45 ± 2.50	12.0-13.00	104.85±%
Product 5	04.25± 0.75	06.50- 7.00	98.77±%

^a Data is expressed as mean ± S.D., (n = 10); ^b Data is expressed as mean ± S.D., (n = 6) ^c Data is expressed as mean ± S.D., (n = 3).

Although there is no official test for hardness, this property need be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard that the disintegration time is prolonged. The recommended value for tablet hardness is 4-8 kg.

All tablets were within the hardness limits. The friability value which is also affected by the hardness value of tablets should be in the range of 0.5- 1% limits. Friability values of the tested tablets were in accepted range.

Dissolution Profile Study: Results of the comparison of the dissolution profiles are presented in figure 3.

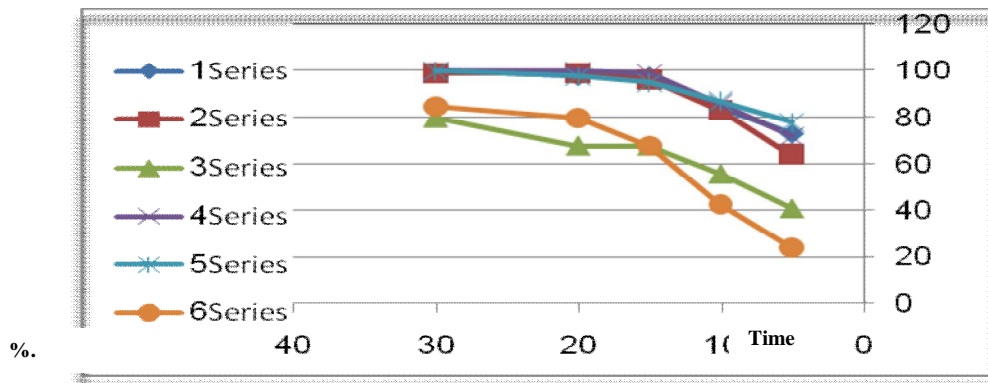


Figure 3: Comparison of the dissolution profiles.

Difference (f1) and similarity (f2) tests were applied to the dissolution data. The difference (f1) factor is proportional to the average difference between the two profiles, whereas similarity (f2) factor is inversely proportional to the average squared difference between the two profiles with emphasis on the larger difference among all the time points. The use of these factors was also recommended for dissolution profile comparison.

According to FDA guide for industry, generally f1 values vary between 0-15 and f2 values vary between 50-100, and should ensure equivalence of the curves [17]. The values of f1 and f2 factors for test products versus reference were calculated from the means of percent dissolved at each time point by using Equations of f1- f2 and listed in Table 3. For tests (1, 3 and 4) versus reference, f1 values indicate that the dissolution profiles of tests (1, 3 and 4) were similar to the profile of reference, and unlike the test product 2-5.

Table 3: The values of f1 and f2 factors for the tested products

Sample	f2 Value	f1 Value
1	68	3
2	27	30.9
3	91	1.32
4	76	1.54
5	24	33.7

DISCUSSION

Several studies in the literature were concentrated on the comparison of the quality of generic with the original compound. One of those studies was about Pharmaceutical quality of ceftriaxone on 34 generic drug products compared with Rocephin. All 34 generics tested failed to meet Roche specifications for Rocephin, with 100 contraventions of the Roche Pharmaceutical standards. The most common failures amongst generic drug products were clarity of dissolution (30 products) and presence of thiotriazinone (33 products) [18].

In another study Pharmaceutical quality of 14 generic isotretinoin products, compared with Roaccutane. Thirteen generic products failed to match Roaccutane in one or more tests and 11 failed in three or more tests. It cannot be assumed that all generic isotretinoin products are as therapeutically effective or safe as Roaccutane [19].

In pharmaceutical quality study on nine generic Orlistat products compared with Xenical[®]. Two generic products failed in tests[20], that means the formulation is widely differed due to the different in excipients, different concentration of excipients, type of diluents (filler) and other adjacent, amount of disintegration agent, amount of surfactant in different factories.

CONCLUSION

As a Conclusions all tested commercial brands of Sitagliptin (100 mg) tablets, were complied with the specific requirements for quality control tests of USP31, namely, the uniformity of weight of tablets, disintegration, dissolution and assay which means the formulations may be similar whereas the result of the test product 2 and 5 were not similar to Januvia in dissolution profile.

It is clear from this study that the tested generic of Sitagliptin are in good quality in most aspect but some concern was in the dissolution profile of some product.

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