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RESEARCH ARTICLE

Assessment of Pharmaceutical Quality Control of three Generic products of Vildagliptin Tablets available in Syrian market

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ABSTRACT:
Vildagliptin is a dipeptidyl peptidase-4 inhibitor used to treat diabetes mellitus. Quality control of pharmaceutical products is an essential operation because it affects on the human health. Evaluation if Vildagliptin local Syrian brand comparing with the reference drug Galvus® (Novartis Pharma). Many physical and chemical quality control tests were applied to Vildagliptin tablets including weight variation, friability, hardness tests in addition to disintegration, dissolution and drug content using modified constitutional chromatography method. The results of physical and chemical tests showed that the tablets within acceptable limits, which allows the use of the tablets of local companies safely. The tests of weight variation, friability, hardness testes were between 182.51±7 to 234.78mg, 0.03 to 0.27% and 7.02±0.43kg/cm^2 to 8.49±0.57kg/cm^2 respectively. All tablet disintegrated within 2.02 min to 7.06 min in distilled water. The drug release (%) in 0.01 HCL and phosphate-buffered saline (PBS) (pH 6.8) after 40 min were between 95.52% to 98.57%. Result assay using HPLC showed that drug content (%) range between 93.29% to 97.24%. The result validation of the analytical method was verified, as the value of the coefficient of determination R was equal to 0.997, which indicates the linearity of this method within the range of concentrations (60-120)%, limit of detection (LOD) is 1.135µg\ml

KEYWORDS: Vildagliptin, Galvus, Quality control, Validation, HPLC.

INTRODUCTION:
Vildagliptin (2S-1-{2- [(3-hydroxyadamantan-1-yl) amino]acetyl} pyrrolidine-2-carbonitrile) is a new oral anti-hyperglycemic agent that selectively inhibits the dipeptidyl peptidase-4 (DPP-4) enzyme. It is used to manage type II diabetes mellitus, where GLP-1 secretion and insulinotropic effects are impaired. By inhibiting DPP-4, vildagliptin prevents the degradation of glucagon-like peptide 1 (GLP-1) and glucose-depended insulinotropic polypeptide (GIP), which are incretin hormones that promote insulin secretion and regulate blood glucose levels. Elevated levels of glucagon-like peptide 1 and glucose-depended insulinotropic polypeptide consequently results in improved glycemic control. This results in improved glycemic control as determined by glycated hemoglobin (HbA(1c)), in addition, an enhancement of pancreatic alpha- and beta-cell function. In clinical trials, vildagliptin has a relatively low risk of hypoglycemia.[1] As first line therapy, DPP-4 inhibitors can be alternative therapeutic option in patients who cannot tolerate metformin because of gastrointestinal adverse events[2].

The object of this study is to monitor and ensure the quality of the various vildagliptin tablets that commercially available in Syrian market in order to assess their quality control. Additionally, if these brands are interchangeable and patients can safely switch from one brand to another or not and which is the best economically. Numerous Vildagliptin tablets brands in Syrian drug market today make a problem of alternative generic brands for physician and the pharmacist. Some

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studies in different countries compared the performance of innovator and generic products of vildagliptin tablets. There are different methods in scientific journals for analysis of vildagliptin, both in pure form and in mixtures with other antidiabetic components. A study was conducted in 2023 to determine vildagliptin content in tablet by reverse phase high performance liquid chromatography (RP-HPLC). All chromatographic conditions that affect vildagliptin analysis were studied. After determining the appropriate chromatographic parameters, the analysis process was validated. The analytical method showed a linear range from 12.5 to 100 µg/ml and the limit of quantification was 1.21 µg/ml. The results of the study can be used as a routine procedure to analyze, control and test vildagliptin stability in tablet formulations.[3]

In 2022, another method for estimation of vildagliptin was developed by using UV spectrophotometry. The absorption wavelength (245.14) nm was selected. The UV spectrophotometric method was found to be linear over the concentration range of 1-5 µg/ml and the study revealed that UV provides a rapid, accurate, precise results for vildagliptin in tablets and it is good recommended for the assay of vildagliptin in marketed pharmaceutical dosage form tablets.[4]

MATERIALS AND METHODS:

Materials:

Vildagliptin standard sample. (Nutra Specialties Private Limited, India) provided by biomed standard laboratories with purity equivalent to 99.8%. Three generic products of 50 mg vildagliptin tablets, also plus original product (Galvus®) produced by Novartis Company (Basel, Switzerland). Hydrochloric acid solution with 37% purity (MERCK, Germany). Distilled water. Acetonitrile for HPLC (Segma, Germany). Phosphoric Acid 0.025 M (Segma, Germany). A group of laboratory tools (assay balloons, flasks, graduate cylinders and pipettes) with different capacity.

Instruments:

Electronic scale produced by radworg (model PS 220.R2 accuracy of ±0.1mg). Hardness measuring device (Erweka, TBH 125TD, Germany,) range 10-300N, accuracy ±1. Friability device L-94 (Pharma test, Germany) model PTF, range 1-1000rpm. Disintegration device L-93 (Pharma test, Germany), range 37±2, accuracy 1 sec. Moisture analyzer (company radwag, Poland), range 0-110g, accuracy 1 mg. HPLC (AGILENT Technologies, 1260 infinity, California). Ultrasound Bath (L18, model PS-80A, German). Dissolution device (Erweka, German). Electronic Beakoles diameter device L-27, range 0-152 mm, accuracy 0.02 mm.

Methods:

A set of physical and chemical tests were applied to the studied brand names of (vildagliptin) (tablets), where the results of these tests were compared between them, and they were also compared with the brand product.

The assay of the content of these brand names of vildagliptin was carried out using the modified constitutional chromatography method.

Quality control tests for pharmaceutical tablets:

Appearance/Description

The control of general appearance involves color, presence or absence of odor, taste etc[6]. The test was procedure out on 20 tablets.[5]

Thickness and diameter:

Measurement Involves of the measurement of size and shape. Tablets thickness varies with particle size distribution and packing of the powder mix being compressed and with tablet weight. There is no tablet thickness limit provided by USP. Tablet thickness is controlled by the in-house specifications and is usually controlled at the range of ±5% from standard values [6]. The thickness test was procedure out on 10 tablets of all dosage forms that were worked on using the Electronic Beakoles device. It is measured in mm. There are many factors that affect the tablet thickness like: tablet weight, die filling, Granules size.

Uniformity of weight:

This test is applicable for uncoated and film coated tablets. For this test according to BP 20 tablets for each of three generic tablets were weighting individually using an electronic balance then calculating the average weights and comparing the individual tablet weights to the average. The difference in the two weights was used to calculate weight variation by using the formal range in the BP. As per BP the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation as shown in Table 1 and none deviates by more than twice that percentage[7]. The weight uniformity test was carried out on all vildagliptin variants, and the deviation in the weight of each sample from the mean weight was calculated and compared with the allowed constitutional proportions.

Table 1: uniformity of weight:

Average weight of tablets	Deviation	Number of tablets
Less than 80mg	±10 ±20	Minimum 18 Maximum 2
80 mg to 250mg	±7.5 ±15	Minimum 18 Maximum 2
More than 250mg	±5 ±10	Minimum 18 Maximum 2

Tablet mechanical strength tablet:

Hardness Test:

Hardness may be defined as the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling. Tablet hardness has been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression[8]. There are different devices used to test hardness like: Monsanto tester, Pfizer tester[8]. The force of fracture is recorded in kilogram. The test is applied to 10 tablets.

Friability Test:

For tablets with a unit weight equal to or less than 650 mg, we should take a sample of whole tablets corresponding as near as possible to 6.5g as USP (2021) mentioned. For tablets with a unit weight of more than 650mg, a sample of 10 whole tablets should be taken.[9]

10 tablets of vildagliptin were put in the device at 25 rpm for 4 minutes.

-It is determined by the following formula:

Friability = $(Iw - Fw)/Iw \times 100\%$

where, Iw = total initial weight of tablets;

Fw = total final weight of tablets.

-As stated by USP if conventional compressed tablets that loss less than 0.5% to 1% (after 100 revolutions) of their weight are generally considered acceptable.

Disintegration Test:

The USP disintegration apparatus consist of 6 glass tubes that are 3 inches held against a 10-mesh screen at the bottom of the basket rack assembly. apply the appropriate procedure to 6 dosage units. The disintegration tester also includes a device for the vertical movement of the basket rack assembly[10] .One tablet is placed in each tube of the disintegration apparatus in specified medium at 37 C. At the end of 15 minutes time limit, the tablet should disintegrate completely. If one or two tablets fail to disintegrate completely, the test should be repeated to 12 additional tablets. The acceptance is when not less than 16 of the totals of 18 tablets tested are disintegrated.[11]

The disintegration test was carried out on six dose units of each studied drug formulation, where the A test was applied to the tablets (diameter less than 18 mm).

Dissolution test:

In - vitro release profile of formulated Vildagliptin tablet Drug release studies were done by using USP type II apparatus (paddle type)[12].

900ml of dissolution medium (0.01N HCl) was transferred into glass vessel and the temperature was maintained at 37ºc±2ºC and Speed of Paddle was 50rpm. At regular time interval (5min.) 5ml sample was withdrawn and replaced with fresh dissolution medium. Removed sample was diluted and injected in HPLC and run at 210nm with flow rate 0.3ml/min column temp 35°C.

- Sample Preparation: 6 tablets were taken individually in each dissolution vessel containing 900ml of 0.01N HCl (37°C±0.5) at 50rpm. After 45 minutes, withdrawn 10 ml aliquot of the solution under test and filtered with 0.2µm GHP Acrodisc syringe filter by discarding the first few ml and injected the clear solution. (0.056 mg/ml).
- Mobile Phase preparation: Prepared a mixture of Buffer Solution and Acetonitrile (previously filtered through 0.2µm Nylon membrane filter) in the ratio 85:15 and sonicated to degas.
- Buffer Solution preparation: Dissolved 1.15 g of ammonium dihydrogen orthophosphate and 0.23 g of di-ammonium hydrogen phosphate into 1 liter of purified water. Filtered through 0.2 µm Nylon membrane filter.
- Procedure: Equilibrated the column for about 30 minutes with the mobile phase. Separately injected equal volumes (5µl) of the sample solution into the chromatograph, recorded the chromatograms and measured the response of the major peak.

Determination Assay using HPLC:

Chromatographic Conditions:[13]

Mobile phase:10Mm potassium phosphate buffer PH 7.3 + Acetonitrile (85:15) the mobile phase, flow rate :1.5 ml/minute, the injection volume: 20 microliters, column: C18, detector: UV at a wavelength of 205 nm.

Preparation of mobile phase:

acetonitrile (15%) and phosphate buffer (85%) mixed together as a mobile phase.

Preparation of monobasic potassium phosphate buffer solution, 0.01 M:

1.36g of monobasic potassium phosphate is weighed and placed in a flask. It is dissolved in an appropriate volume of water and then the volume is adjusted to the mark on the flask with water (to 1000ml). The pH is adjusted using 1M sodium hydroxide solution. The resulting solution is filtered.

Preparation of standard Vildagliptin (100) µg/ml:

50.0 mg of accurately weighed Vildagliptin into a 50ml flask then it dissolved in an appropriate volume of mobile phase using ultrasound, then adjusted to the mark with mobile phase and filtered a suitable volume of the solution. 1.0ml of the solution transferred to a 10ml flask and completed the volume to the mark with the mobile phase.

Working method:

20µL was injected of the standard Vildagliptin. The procedure repeated 5 times in a row then the peak area

was recorded, the number of layers, and the resulting peaks. After that 20µL (twice) of each solution sample was injected.

Method validation:

The optimized chromatographic conditions were validated by evaluating linearity, precision, accuracy, limit of detection (LOD) and limit of qauantitation (LOQ), parameters in accordance with the ICH guideline Q2 (R1).[14]

Linearity:

Method linearity was determinated by evaluating the regression curve and is indicated by the square correlation coefficient (R2). Standard solutions of Vildagliptin were prepared in the concentration range of 10–35µg/mL for the determination of linearity. 3 sets of such solutions were prepared. Each set was analyzed to plot a assay curve. Standard deviation (SD), slope, intercept and coefficient of determination (R2) of the assay curves were calculated to ascertain linearity of the method.

RESULTS:

Appearance test:

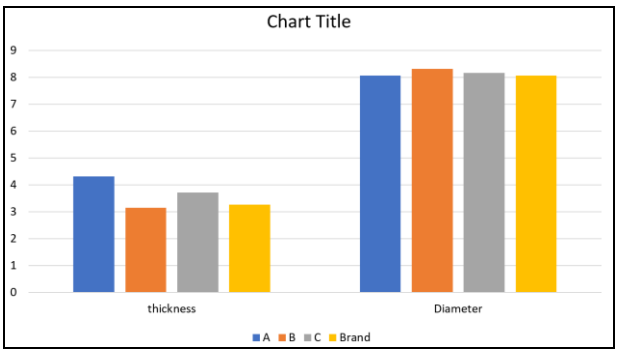
All vildagliptin tablets were shown to be tolerable in appearance. The the tablets were smooth and did not contain cracks indicating cracking, staining or color change.

Table 2. Results of the appearance test

Sr. No	Code	Physical description (shape and color)	Logo	Break line
1.	A	A white tablet with a round shape	NO	No
2.	B	A white tablet with a round shape	NO	Yes
3.	C	A white tablet with a round shape	YES (MPP)	Yes
4.	Brand	A white tablet with a round shape	YES (NVR) and the other face (FB)	No

Thickness and dimensions of tablets:

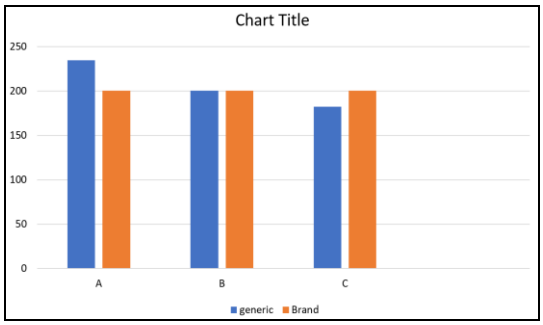
Dimeter was between 8.006 to 8.33mm for all tablets and the thickness was between 3.144 to 4.325mm.



Bar chart 1: Results of thickness and diameter three generic tablets of vildagliptin

Uniformity of weight test:

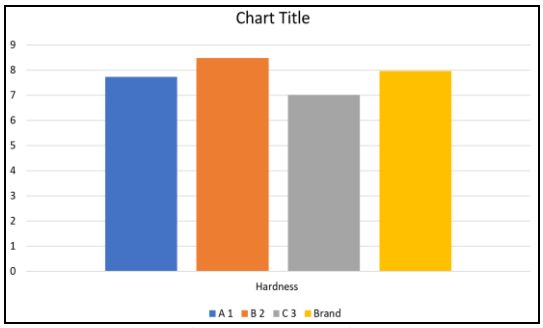
The average weight of tablets was within the range (80-250) mg, so the permissible deviation was (±7.5%) The statistical analysis was carried out with the help of the statistical program using the Student-T test for two independent samples, where the differences at the significance threshold (P value less than 0.05) were considered statistically significant.



Bar chart 2: Results of weight uniformity test of three generic tablets of vildagliptin comparing with brand

Hardness and Friability test:

Results of hardness test were between 7.02 to 8.49 kg/cm^2, Friability results were between 0.03 to 0.27%.



Bar chart 3: Results of hardness test of three generic tablets of vildagliptin comparing with brand

Table 3. Results of the friability test

Code	Friability test
A	0.27%
B	0.03%
C	0.09%
Brand	0.06%

Disintegration test:

The disintegration time was calculated and the table 5 shows the specific time with each preparation.

Table 4. Results of the disintegration test

Batch	Time (min)
A	4.22min
B	7.06min
C	2.02min
Brand	2.99min

Dissolution test result:

Dissolution results showed that all tablets are acceptable according to table.

Table 5. Results for *in-vitro* drug release of immediate release tablet of vildagliptin

Time (min)	A Q%	B Q%	C Q%	Brand Q%
10	86.28%	86.60%	89.33%	87.26%
20	89.43%	89.75%	92.48%	90.41%
30	90.41%	92.09%	94.82%	92.75%
40	95.52%	95.84%	98.57%	96.50%

Results showed that the release rate of all the tablets was greater than 85%. f1 values vary between 0-15% and f2 values vary between 50-100%.

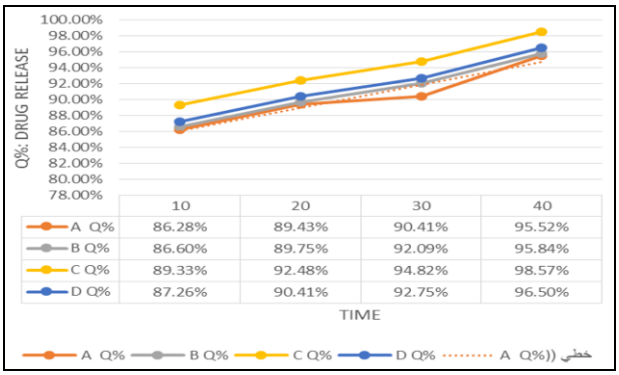


Figure 1. -Dissolution profiles comparison of vildagliptin Syrian brand names and the reference preparation(D)

Assay results:

The results were between 93.279% to 97.244%.

Table 6. The results of HPLC assay

Batch	Absorbance	Retention time	Drug content %
A	819.1	16.132 min	94.84%
B	856.4	16.096 min	97.24%
C	811.3	16.097 min	93.30%
Brand	833	16.105 min	94.84%

Validation results:

The validation of the analytical method was verified, as the value of the coefficient of determination R was equal to 0.997, which indicates the linearity of this method within the range of concentrations (60-120%). The values of (RSD% less than 2%) for the absorbance ratios of the standard Vildagliptin which confirms the accuracy of this method. The values of the limit of detection (LOD) is 1.1351ml/µg, limit of quantitation (LOQ) is 3.7835ml/µg.

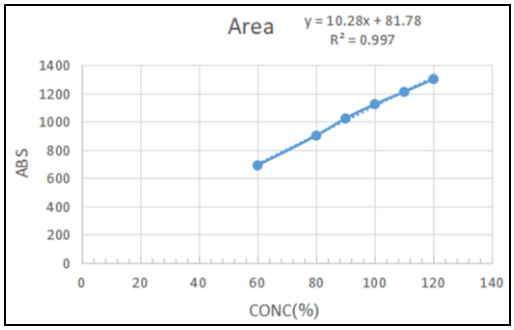


Figure 2. Plotting graph of absorbance versus corresponding concentrations

DISCUSSION:

Appearance test:

The tablets were similar to the standard preparation, which indicates that the local pharmaceutical companies used similar preparation molds among themselves and similar to the international company (Novartis), and this in turn would lead to similarity in the dimensions of the tablets. There are no inscriptions or symbols of company A and B tablets, unlike company C and the reference product (Brand). The difference in colors, patterns, and symbols between the different preparations is due to manufacturing techniques and considerations specific to each pharmaceutical company. It is assumed that these technical differences do not lead to differences in the level of physical and chemical properties of the preparations, their quality, and their conformity with constitutional requirements.

Determining the dimensions of tablets:

Results of the statistical analysis when conducting a T-test for two independent samples, which compares the reference product with the local companies in terms of average diameter, showed that for company A there was not any difference from standard, while for company B the difference was in favor of it and also for company C the difference was in favor of it.

As for the statistical analysis of the average thickness between the reference product and the local companies, results showed that for company A, the difference was in favor of company B, the difference was in favor of the reference product, and company C, the difference was in favor of it.

Mechanical resistance tests for Vildagliptin products:

Results of the statistical analysis show that there is no difference in the average hardness values of the studied samples, so only Company C showed an important statistical difference, and the difference was in favor of the reference product. The study showed that all the tested tablets from the local companies and the tablets of the reference preparation passed the friability test where they showed good friability (less than of 1%) , and the A product tablets had the highest rate of friability (0.27%). As for results of the statistical analysis of the friability test, there are statistically significant differences. When comparing the local companies with the standard product, it showed that for product A, the difference was in favor of it. As for company B, the difference was in favor of the standard product. As for company C, the difference was in its favor.

Uniformity of weight:

Results of the statistical analysis which compares the reference product with the local companies in terms of average weights, showed that for company A the difference was in favor of it, while for company B there

was no difference and for company C the difference was in favor of the reference product.

Disintegration test:
Results of the statistical analysis using the T-test showed that there were statistically significant differences between the local companies and the reference product with the disintegration test, so the average statistical differences in company A and company B had a clear difference in terms of the average disintegration from the standard product while it was between the average disintegration of the company C is closest to the standard product.

Dissolution test:
We note that all studied preparations passed this test, as the Q% values were greater than the constitutionally permissible value for vildagliptin (85%) at the end of the test. The dissolution rate was the C product was the best (98.57%). Also, as the percentage released from the C tablets was closest to the Q ratio of the reference product.

Profile dissolution comparison:
Results of the statistical analysis using T show that there are no statistically significant differences between the average values of dissolution (at 40 minutes) for the samples of the two preparations studied for each of pharmaceutical companies A, B and C .

The largest value of the similarity factor was for company C tablets, and this confirms that its dissolution behavior is the most similar to the reference preparation.
For company A the values of F1 and F2 are within the range and therefore the product of this company is pharmaceutically equivalent to brand.

For company B the values of F1 and F2 are within the range and therefore the product of this company is pharmaceutically equivalent to brand.

For company C the values of F1 and F2 are within the range and therefore the product of this company is pharmaceutically equivalent to brand.

Since the values of f1, f2 are within the range required for generic medicines, and therefore the medicines are bioequivalence and similar to the brand name, and therefore the patient can switch between these medicines.

CONCLUSION:

This study was conducted to evaluate and control the quality of vildagliptin tablets, which were studied and taken from three locally manufactured pharmaceutical companies in Syria, which were coded A, B, and C. Then, we made a comparison between the preparations from each company, and they were compared with the reference preparation (Galvus ®) manufactured from By Novartis shows the following:

All pharmaceutical generic products of vildagliptin passed the physical and chemical tests applied to them in this study, but results of these tests differed between them and when compared with the reference product.

The tablets of the local company C were the best among all the preparations due to the similarity of their dissolution behavior with the reference preparation, and they passed all quality tests and achieved close results to results of international drug.

Consistency of production of companies and compatibility of vildagliptin preparations within the same pharmaceutical company, according to the statistical study on results of the tests (uniformity of weight, uniformity of dose units, assay "according to HPLC" and dissolution) applied to the preparations of each company separately. This was with the exception of the preparations of companies A and Brand only their respective dissolution test results did not correspond.

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