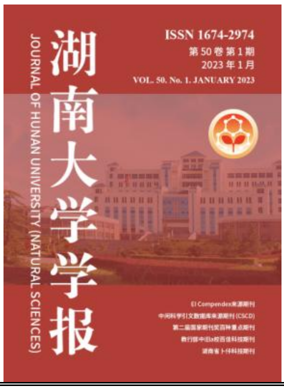

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Dissolution Testing and Content Uniformity Analysis for Metformin Tablets Using Vildagliptin as an Internal Standard

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Abstract: Poor-quality medicines, brand or generic, do not meet acceptable standards. Further studies must explore the status of generic medicines in Qatar and the region, especially during the GCC crisis. The research goal is to assess whether the multi-sourced antidiabetic medication, Metformin Hydrochloride (MH) tablets marketed in Qatar and other selected worldwide locations fulfill the compendial quality control parameters and in vitro bioequivalence/interchangeability requirements. Could we safely replace branded Glucophage® with generic MH without compromising the patient's interest? This laboratory experimental study assessed the quality control parameters and in vitro bioequivalence/interchangeability requirements of sixteen marketed products of MH tablets from 11 countries in addition to 33 MH products from Qatar's market based on the US Pharmacopeia (USP 34) guideline recommendations. Content analysis test showed that the minimum amount was 96.9% in product S10 from the International samples and 97.1% for both Neomet (Q-N.m-1) and Glucophage (Q-G.Ph-2) from Qatar's samples, while the maximum amount was 103.3% in product S4 (Formit 500) from the international market and 101.8% in product Q-Di-4, which is Dimet -500 from Qatar's market. The rapid increase in the percentage of the drug release is noticed in products (S2-S6-S8-S9-S10-S12-S13-s15-S16–(Q-N.m-1)-(Q-Di-1)-(Q-Di-3)-(Q-D.ph-1)-(Q-D.ph-3)-(Q-M.ph-1)-(Q-M.ph-2)-(Q-G.m-3)) as they achieved the acceptance limit at the first time point (15 min). However, the products that showed the slowest release are (S4-S11-S14-(Q-D.Ph-3)). But, eventually, at 45 min, all the products passed the dissolution test. similarity factor results revealed that the Glucophage (S15) and (Q-G.Ph-5) were found to be the most similar products to the innovator brand Glucophage® (France) with the highest similarity factors (f_2 = 91.1%) and (f_2 = 90.0%) respectively. This research has confirmed that not all the generics are exchangeable with the reference product Glucophage®.

Keywords: Metformin, bioequivalence, interchangeability, Qatar, dissolution.

以维格列汀为内标对二甲双胍片进行溶出度测试及含量均匀度分析

摘要：劣质药品，无论是品牌药还是非专利药，都不符合可接受的标准。进一步的研究必须探讨仿制药在卡塔尔和该地区的状况，尤其是在海湾合作委员会危机期间。研究目标是评估在卡塔尔和全球其他选定地点销售的多来源抗糖尿病药物盐酸二甲双胍(MH)片剂是否满足药典质量控制参数和体外生物等效性/互换性要求。 我们能否在不损害患者利益的情况下，

用仿制药 MH 安全地替换品牌噬菌体®？本实验室实验研究根据美国药典(美国药典 34)指南建议评估了来自 11 个国家的 16 种已上市 MH 片剂产品以及来自卡塔尔市场的 33 种 MH 产品的质量控制参数和体外生物等效性/互换性要求。含量分析测试表明，国际样品中产品小号 10 的最低含量为 96.9%，卡塔尔样品中纽美特（Q-N.m-1）和噬菌体（Q-G.Ph-2）的最低含量为 97.1%，最高含量为 103.3%来自国际市场的产品小号 4 (格式 500)和来自卡塔尔市场的产品 Q-Di-4 即迪梅特-500 的 101.8%。在产品(S2-S6-S8-S9-S10-S12-S13-s15-S16–(Q-N.m-1)-(Q-Di-1)-(Q-Di-3)-(Q-D.ph-1)-(Q-D.ph-3)-(Q-M.ph-1)-(Q-M.ph-2)-(Q-G.m-3))因为他们实现了第一个时间点（15 分钟）的接受限度。但是，发布最慢的产品是(S4-S11-S14-(Q-D.Ph-3))。但是，最终，在 45 分钟时，所有产品都通过了溶出度测试。相似因子结果显示，噬菌体(小号 15)和(Q-G.Ph-5)被发现是与创新品牌噬菌体®（法国）最相似的产品，具有最高的相似因子（f2 = 91.1%）和（ f2 = 90.0%)。这项研究证实，并非所有仿制药都可以与参考产品噬菌体®互换。

关键词：二甲双胍，生物等效性，互换性，卡塔尔，溶出度。

1. Introduction

Qatar is continuously going through healthcare reform and improvement. It has continuously increased its investment in health care to achieve a better-quality healthcare system [1].

Tremendous amount of healthcare funds in Qatar is currently spent on branded original medicines, which is increasing. Spending more on medicines could mean less money for other healthcare or non-healthcare services. Currently, the world is experiencing an economic crisis and Qatar is not excluded. With the increasing financial pressure on rational spending, healthcare funders such as the government are, therefore, looking for ways of controlling the costs of medicines while still ensuring that patients get the effective medicines they need.

One approach that health funders in Qatar can use is the usage of generic medicines. The preference of brand originators wastes huge resources that could have been used more efficiently on quality generic medicines and thus save the public money [2]. Few previous recent studies conducted in Qatar have indicated that both pharmacists and lay people have a low level of knowledge and perception of poor quality of medicines [3, 4].

A study revealed that two out of ten tested antidiabetic products, only Glucophage® (Qatar), Diaphage®, Diamet® (Palestine), Glucophage® (Oman), Glucomet®, and Glucophage® (Thailand) can be considered interchangeable with the chosen innovator brand (Glucophage®) [5]. Although one recent study reported that switching originator brand medicines to generic equivalents could save public money [6], further studies are still required to explore the real status of generic medicines in Qatar and the region. The focus of this study was on antidiabetic medicines, namely Metformin Hydrochloride (MH), due to the high prevalence of diabetes mellitus type II in the country and the popularity of prescribing MH among physicians.

The proposed study was designed to evaluate and compare different brands of MH from Qatar and other countries by testing the dissolution rate and absolute drug content and calculating the similarity factor. The study is expected to answer the following questions: Do the multisource MH tablets marketed in Qatar and other selected regional and worldwide locations fulfill the compendial quality control parameters and in vitro bioequivalence/interchangeability requirements? Could we safely replace branded Glucophage® with generic MH without compromising patient interest? How can, we be sure? To answer the aforementioned research questions, we conducted the study through quality control testing and other compendial quality assurance and laboratory analysis phases [7].

2. Research Methods

2.1. Study Design

This was a single-blinded laboratory study. Sixteen marketed products of immediate-release MH tablets from 11 international locations, in addition to 33 products of MH tablets from Qatar's market, were assessed using the guidelines in the United States Pharmacopoeia related to drug content, dissolution studies, and similarity factor analysis. Tested immediate-release products were blinded during the method, and a specified code was given to each drug.

The non-Qatar samples were given the code (S1-S15+MX), while the new samples from Qatar's market were given the code (Q1-Q32). All the tablets were labeled to contain 500 mg, except S1, S9, and Q33 labeled to contain 850 mg.

2.2. Materials

A pure active ingredient sample of MH was purchased from PCCA, London, Ontario, Canada. A pure active ingredient sample of Vildagliptin was purchased from Megafine Pharma, Mumbai, India. Potassium dihydrogen phosphate was purchased from VWR, Belgium, Sodium dihydrogen orthophosphate dihydrate $NaH_2PO_4.2H_2O$ manufactured by Fisher Scientific, UK, Sodium hydroxide NaOH was purchased from Merk, Germany, and HPLC Acetonitrile was purchased from VWR, France. Water purified from the Milli-Q system (MILLIPORE/Merk) was used for preparing the mobile phase.

2.3. Methods of Analysis

2.3.1. UPLC Parameters

Waters-Acquity Ultra Performance Liquid Chromatographic system equipped with Auto Sampler, PDA detector, detection at a wavelength of 210 nm, column XBridge BEH C18 (100 x 4.6 mm), 2.5 µm, a mobile phase of Phosphate buffer of pH = 5.0 and Acetonitrile in the ratio (92:8) v/v at a flow rate of 0.3ml/min were used. Injection Volume = 1 µl. The temperature of the column oven and autosampler was maintained at 25^{C} [8].

2.3.2. Dissolution Apparatus Parameters

Agilent Technology 709-DS dissolution apparatus was used; Phosphate buffer PH = 6.8; Vessel temperature = 37°C; Sample volume = 5 mL; Prime volume = 5 mL; Replacement volume = 6 mL; waste drop volume = 1ml; Media volume = 1000 mL; Spinal = 100 RPM (round per minute); Apparatus: basket; Programmed time points: 15, 30, 45, and 60 min.

2.4. Procedures and Preparations

- Prepare phosphate buffer PH = 5 as a solvent.
- Prepare Mobile Phase (phosphate buffer PH = 5: Acetonitrile) in a ratio (98:2) as a diluent.
- Prepare phosphate buffer PH = 6.8 as media in the dissolution test.
- Prepare (1 mg/ml) stock solution of the internal standard (Vildagliptin) dissolved in deionized water.
- Prepare (1 mg/ml) standard stock solution of MH dissolved in the solvent.
- Prepare the calibration curve: working standards solution containing 10–200 µg/ml of MH stock solution was prepared. In addition to a constant amount of the stock solution of Vildagliptin (internal standard) (equivalent to 1 mg/ml). Then, up to volume with the mobile phase. 0.1 µl were injected (3 injections for each concentration) under the reported UPLC parameters. The area ratio (Area MH/Area Vildagliptin) was calculated. The concentration against area ratio was plotted, and the regression (R^2) value with the equation was determined and used to calculate the concentration of unknown samples.

- *Prepare the content samples*

To determine the content of MH in the tablets, 20 tablets from the product were weighed separately. The average weight was calculated. Then, the 20 tablets were crushed and finely powdered until obtaining a homogeneous powder using a glass mortar and pestle. A portion of the powder equivalent to 50 mg of MH was transferred to a 50 mL volumetric flask, 5.0 ml of solvent was added, and the solution was shaken very well, then up to volume by solvent. Then, 2.0 ml from the stock and 2.0 ml of (IS) were diluted to 20 ml (VF) and up to volume by using the diluent. The solution was filtered using a 0.2um Nylon filter and injected into UPLC parameters. The area ratio was recorded, and the concentration was calculated from the calibration curve equation.

- *Prepare the dissolution samples*

Six tubes were prepared per sampling time and labeled (A-F) with the symbol of the product and the time point sampling. They put the tubes on the valves of the sampling system. The dissolution test was run according to the dissolution parameters. After finishing the dissolution, 6 volumetric flasks (10 mL) were prepared for each time point and labeled from (A-F). 2 mL from each sample was transferred and placed in the volumetric flask, 1 mL from Vildagliptin stock was added; then, the volumetric flask was filled till 10 mL with the mobile phase. The diluted samples were filtered using 0.2 um Nylon filters and then filled in the UPLC`s vials. The test was run according to the UPLC parameters. The area ratio was determined between the MH`s area and Vildagliptin`s area, the equation from the calibration curve. X = (Y-0.0924)/0.0482 was used to calculate the concentration. The Sigma plot program was used to plot the time vs. release %.

- *Determining f_2 value*

The dissolution profile for each product and for the reference product was determined, then by using the dissolution values for the tested curve and reference curve, the f_2 value was calculated using a similarity factor program, which calculated the value according to the following equation

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

where f_2 is the similarity factor, n is the number of time points, Rt is the dissolution value of the reference product at the t time point, Tt - the dissolution value of the tested product at the t time point. An f2 value between 50 and 100 suggests that the two dissolution profiles are similar. This method was developed in-house and has been validated according to the ICH Guideline [9–11].

2.5. Sample Selection

Sixteen marketed products of MH tablets were collected from 11 countries in addition to 33 products of MH tablets collected from Qatar's market within 4 months (1 brand + 5 generics).

The main steps of the research process are summarized in Fig. 1.

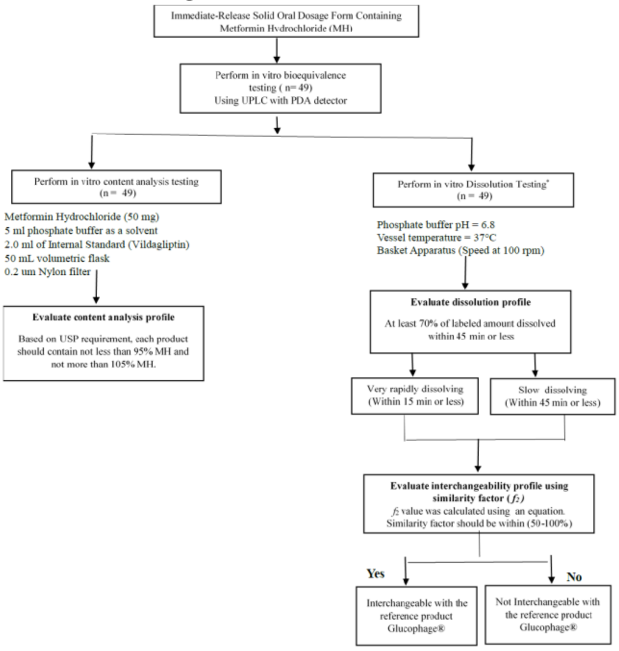

Fig. 1 Flowchart of the research methodology (Elaborated by the authors)

* Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product SIF-simulated intestinal fluid and SGF-simulated gastric fluid.

3. Results

3.1. Calibration Curve

From the calibration curve, shown in Fig. 2, a high correlation coefficient ($R^2 = 0.9995$) was obtained. The calibration curve equation was used to calculate the content amount of MH and the release % of Metformin tablets after dissolution as follows:

$X = (Y- 0.0924)/0.0482$

X - is the concentration of MF;

Y - is the area ratio at each time point obtained.

The equation shows a good linear relationship between the MH concentration and area ratio at each time point. The correlation coefficient r^2 value is very close to 1 and reflects the good correlation between the concentration and the area ratio.

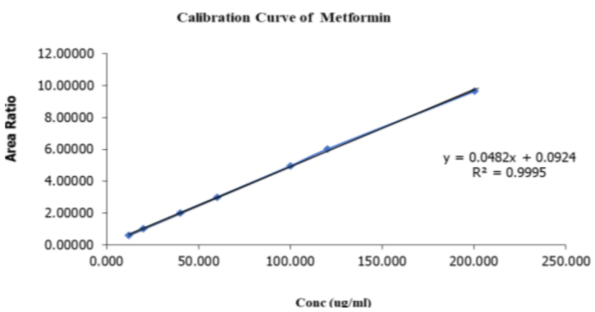

Fig. 2 The calibration curve of Metformin Hydrochloride (Elaborated by the authors)

3.2. Content Analysis Test

Regarding content analysis tests, Table 1 shows the amount of MF in each product. According to the USP, each product should contain not less than 95% MH and not more than 105% MH.All the products have met the USP requirement, the minimum amount was 96.9% in product S10 from non-Qatar (the International) samples and 97.1% for both Neomet (Q-N.m-1) and Glucophage (Q-G.Ph-2) from Qatar's samples, while the maximum amount was 103.3% in product S4 (Formit 500) from the international market and 101.8% in product Q-Di-4, which is Dimet -500 from Qatar's market.

Table 1 Results of the content analysis test (Elaborated by the authors)

International samples (16 samples)	
Drug code (name)	**Content%**
S1 (Brot 850)	99.4
S2 (Metfor 500)	98.4
S3 (Dimet-500)	98.4
S4 (Formit 500)	103.3
S5 (Metforal)	102.1
S6 (Glymet)	99.8
S7 (Siofor 500)	99.6
S8 (Dialon)	99.3
S9 (Glucomet)	99.3
S10 (Cidophage)	96.9
S11 (Glucophage)	99.5
S12 (Glucophage)	99.6
S13 (Poliformin)	100.0
S14 (Siamformet)	97.8
S15 (Glucophage)	100.4
S16 (Glumet DC)	99.1

Samples of Qatar (21 samples)	
Glucophage (7 samples)	
Drug code	**Content%**
Q-G.Ph-1	100.6
Q- G.Ph-2	97.1
Q- G.Ph-3	99.6
Q- G.Ph-4	101.4
Q- G.Ph-5	100.9
Q- G.Ph-6	100.6
Q- G.Ph-7	101.3
	Avg = 100.2
	Rsd = 1.67%

Neomet (2 samples)	
Drug code	**Content%**
Q-N.m-1	97.1
Q-N.m-2	97.3
* RSD: cannot be calculated for 2 samples as Neomet is out of the market	Avg = 97.2 Rsd = *

3.3. Dissolution Profile

Based on USP, the release should be more than 70% within 45 min. As a result, all the products meet the acceptance of the USP 34 requirement and pass the dissolution test. The rapid increase in the percentage of the drug release is noticed in products (S2-S6-S8-S9-S10-S12-S13-S16–(Q-N.m-1)-(Q-Di-1)-(Q-Di-3)-(Q-D.ph-1)-(Q-D.ph-3)-(Q-M.ph-1)-(Q-M.ph-2)-(Q-G.m-

3)) as they achieved the acceptance limit at the first time point (15 min). However, the products that showed the slowest release are (S4-S11-S14-(Q-D.Ph-3)). But, eventually, at 45 min, all the products passed the dissolution test.

Dissolution profiles of international samples

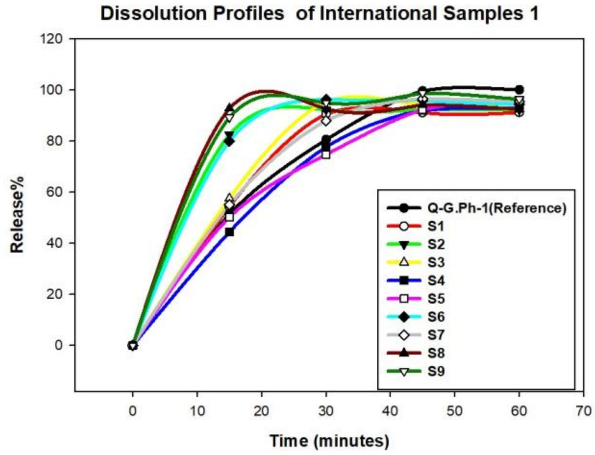

Fig. 3 Comparative dissolution profiles of MH tablets coded + the reference (Elaborated by the authors)

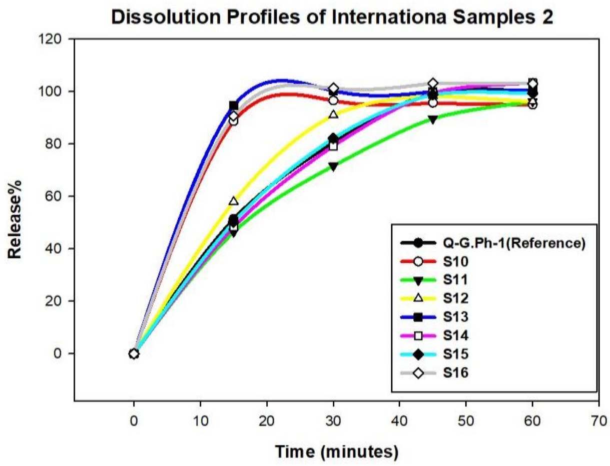

Fig. 4 Comparative dissolution profile of MF tablets coded + the reference (Elaborated by the authors)

Dissolution profiles of Qatar's sample

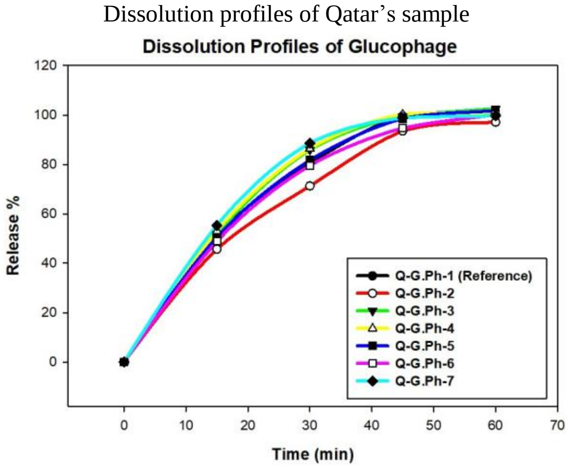

Fig. 5 Comparative dissolution profile of Glucophage tablets (Elaborated by the authors)

3.4. Reference Dissolution Profile

A Glucophage dissolution test was performed to use its percentage release values as a reference in the calculation f_2 similarity factor. It was noticed that the reference dissolution profile was similar to the products (S1-S4-S5-S7-S11-S12-S14-S15-(Q-Di-2)-(Q-G.m-1)-(Q-G.m-2)).

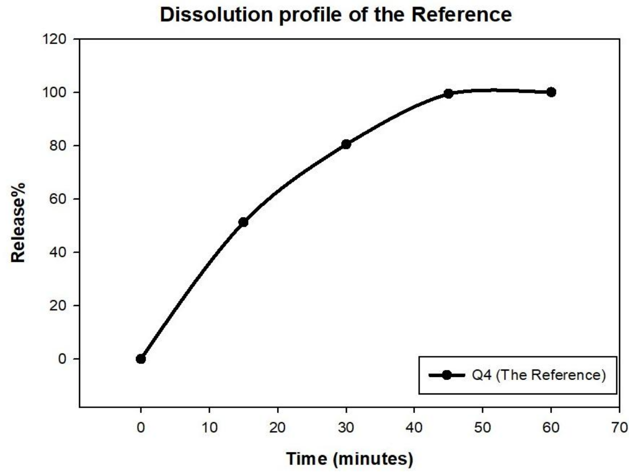

Fig. 6 Reference dissolution profile of Glucophage (Elaborated by the authors)

3.5. Similarity Factor, f_2

f_2 value is calculated according to the reference product Q- G.Ph-4.

Table 2 Similarity factor (Elaborated by the authors)

Drug code	**f_2 Similarity factor %**
International Samples	
S1	54.5
S2	37.8
S3	41.8
S4	62.9
S5	63.7
S6	38.2
S7	64.7
S8	32.8
S9	34.6
S10	34.3
S11	56.4
S12	59.1
S13	31.2
S14	80.1
S15	91.1
S16	32.4
Samples of Qatar	
Glucophage	
Q-G.Ph-1	Reference
Q-G.Ph-2	59.5
Q-G.Ph-3	75.0
Q-G.Ph-4	74.8
Q-G.Ph-5	90.0
Q-G.Ph-6	76.4
Q-G.Ph-7	66.6

Table 2 shows the similarity factor which was calculated for each product using Q-G.Ph-4 Glucophage as a reference in the following equation:

$$f_2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \bullet$$

100}

If the similarity factor is within 50-100% we can say that the product is similar to the reference brand, and they can be changeable with the reference product. As expected from dissolution profile (S1- S4-S5-S7-S11-S12-S14-S15–(Q-G.m-1)–(Q-G.m-2)) have f_2 value over 50 %. Interestingly the product (S15) showed the highest similarity factor among the other products. While the other products didn`t achieve the similarity factor requirements. This was consistent with the dissolution profile.

4. Discussion

Metformin Hydrochloride belongs to a class of drugs called biguanides. It is available over the counter in many nations and used primarily to treat type II diabetes and other non-FDA labeled indications. It can be used on its own or combined with other drugs. It aims to decrease glucose production in the liver, consequently lowering the glucose level in the blood. It is available in the pharmaceutical market of Qatar in different brands and generics, however, after the crisis in the GCC region, its presence has been limited to Glucophage® (the brand) and a few generics (Dimet-500®, Neomet®, Metaphage®, Diaphage® and Glymet®), although it is still hard to find those generics beside that some of them were missed after some time. Therefore, it is very important for the health care providers and patients to know that those generics and brands are similar in their efficacy.

A generic drug product must demonstrate that it is bioequivalent to a reference product that has received marketing authorization based on clinical trials, even though some global regulatory authorities differ from one another [12-14]. The establishment of surveillance systems for generic products already on the market has been encouraged [15] because there have been sporadic post-marketing quality fears [16]. Direct bioequivalence investigations are scarce, even though several clinical studies failed to find significant differences between reference and generic products [18–19].

In this study, 33 different immediate-release MH tablets from the Qatar market, besides 16 different MH products from 11 countries were involved in dissolution and content analysis tests to assess their bioequivalence. In addition, the assessment includes the calculation of the similarity factor to determine their interchangeability [20]. The study helps to find out whether the brands and generics in the Qatar market within Qatar circumstances meet the USP requirement or not? Could we safely replace branded Glucophage® with generic MH without compromising patient interest?

Similar studies have been performed to assess the bioavailability/interchangeability of MH. According to study [21] that was conducted in Jordan, five different MH brands were analyzed according to the British Pharmacopeia (2007) monograph. Glucophage, Glymet, Metforal, Diaphage, Formit were assessed, and the results showed that all the tested products met the British Pharmacopeia (BP) 2007 requirements apart from Metforal®. Glymet® was the only drug that is the bioequivalent in terms of dissolution to the reference drug. Thus, Glymet® is interchangeable with the reference MH.

Moreover, [22] evaluated six different MH brands that were available in the Saudi market. All the tested six brands were bioequivalent and fulfilled official and non-official USP Pharmacopoeia standards except for Glucare®. Thus, it is safe to switch from one brand to other. Moreover, a randomized, open, single-dose, three-period crossover study was conducted by [23]. This study compared MH 500 mg to 4 different reference MH products [23]. Analysis of the study revealed that the reference MH products were bioequivalent.

In our study, the percentage content of MH products was evaluated, and the results showed values within the 95% to 105% range that the USP monograph specified. Regarding the non-Qatar' market, the minimum concentration was for Cidophage® with 96.9%, while the maximum concentration was for Formit 500® with 103.3%. Meanwhile, in the Qatar's market, the minimum concentration was for Glucophage® (Q-G.Ph-2) with 97.1% and Glymet® (Q-G.m-1) with 97.2%. As well both batches of Neomet® ((Q-N.m-1)-(Q-N.m-2)) were with low concentration of (97.7%-97.3%) respectively. A similar study was conducted in Jordan for 5 brands of MH [21]. All of the MH products, except for Metforal® (91.9%), were clearly in compliance with the BP standards in terms of content analysis.

In vitro dissolution tests for immediate-release solid oral dosage forms, such as tablets and capsules, are employed based on this general concept to evaluate the lot-to-lot quality of a drug product and guarantee continued product quality and performance following specified modifications, such as adjustments to the method, site, or scale of the manufacturer [24]. This study aimed to compare the dissolution rate between the brand Glucophage® and its generics to ensure continuing product quality.

Firstly, the release % of all the MH tablets at 45 minutes achieves the USP 34 requirements, which states that it should be more than 70%, although the rate of the release was different among the products. For an example, Diaphage® from Jordan has the slowest release, which means it goes slowly into the solution. On the other hand, Metaphage® from Kuwait has the fastest release and it goes fast into the solution. Our study showed that all the MH tablets successfully passed the dissolution test. This means that within 45 minutes, the drug dissolved completely and was ready for absorption and producing its pharmacological effect. The dissolution profiles also show consistency in the release of Glucophage®, Neomet®, Glymet® and Metaphage®. On the contrary, Dimet-500® and Diaphage® dissolution profiles show significant variation. The different dissolution profile of Diaphage® was (Q-D.Ph-3) produced in 2018, while ((Q-D.Ph-1)-(Q-D.Ph-2)) and similar profiles were produced in 2015 and 2016, respectively.

f_2 is the most basic of the various approaches investigated for comparing dissolution profiles Moore and Flanner provided a model-independent mathematical method to compare the dissolution profile [17]. Based on FDA recommendations, f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. Interestingly, the product (S15) showed the highest similarity factor among the other products. Only ten products (S1-S4-S5-S7-S11-S12-S14-S15–(Q-G.m-1)–(Q-G.m-2)) have f_2 values over 50%. The other products did not achieve the similarity factor requirements. In [21], f_2 was 74.3 for Glymet and 39.4 for Diaphage. According to the similarity factors results, Glymet showed a comparable dissolution profile to the reference Glucophage®, however Diaphage did not [21].

5. Conclusion

Based on this study of 49 selected oral immediate-release MH generic products marketed in Qatar and other worldwide locations, we can conclude that all the MH generics meet the US Pharmacopoeia requirements in terms of content analysis and dissolution. Furthermore, all MH products had percent dissolved within 95% to 105% that the USP monograph specified. Moreover, all the brands had more than 70% dissolved within 45 minutes. Dissolution profiles revealed differences between the MH generic products reflected by similarity factor values. Ten products (S1-S4-S5-S7-S11-S12-S14-S15–(Q-G.m-1)–(Q-G.m-2)) were equivalent to the originator Glucophage® because they had f_2 value over 50 %.

5.1. Implications of the Study

The fact that there are already some substandard MH brands on the market proves the necessity of strong regulatory guidelines for testing the quality of medications. In addition, pharmaceutical products' post-marketing evaluations could be regarded as the gold standard for ensuring product quality.

5.2. Strengths and Limitations of the Study

The current study is an in vitro bioequivalence study, which offers advantages over an in vivo investigation in terms of speed, cost, and ethical considerations. On the other hand, few limitations were found. We only looked at non-combinational MH products. However, given that the BE standards for combinational and non-combinational products are identical, it is reasonable to assume that the outcomes apply to combinational products.

5.3. Recommendation and Future Research

The current in vitro study results can give an idea of the in vivo bioavailability, but more in vivo bioavailability studies should be carried out. Additionally, to learn more about the physiochemical characteristics of MH, it is important to test other quality control metrics such as friability, hardness, and disintegration. Moreover, our results may not be generalizable to other solid immediate-release MH products on the market since the combinational MH products were not assessed.

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