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Original Article

COMPARATIVE *IN VITRO* DISSOLUTION STUDY ON METFORMIN MARKET PRODUCTS USING DIFFERENT DISSOLUTION APPARATUSES

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ABSTRACT

Objective: This study was proposed to evaluate and compare the *in vitro* dissolution profiles of six Metformin Hydrochloride (MH) market products.

Methods: Different dissolution apparatuses (USP apparatus II, IV and beaker method) were used to evaluate the dissolution profiles (in phosphate buffer, pH 6.8) of two immediate release (IR) generic products of Metformin Hydrochloride (MH): Cidophage® 1000 mg (G1, Egyptian market) and Metformin arrow® 1000 mg (G2, French market) with respect to the reference products named Glucophage® 850 mg (R1, Egyptian market and R2, French market). In addition to a generic controlled-release (CR) product; Cidophage Retard® 850 mg (G3) versus the reference product; Glucophage XR® 1000 mg (R3) (both from Egyptian market). Dissolution efficiency (D. E.) and the similarity factor (f_2) were calculated. Weight uniformity, hardness, tablet dimensions and MH content were measured.

Results: Results of the three apparatuses showed that MH IR products studied (reference and generics) did not meet the 75% USP 30 specifications for MH dissolved at 30 min. For MH CR products, Glucophage XR® did not fulfill the USP release criteria, while Cidophage Retard® did. USP apparatus IV revealed the highest sensitivity and discriminative capability.

Conclusion: Generally, MH IR generics (G1 and G2) might be interchangeable with the innovator product (Glucophage®). However, Cidophage Retard® might not be interchangeable with Glucophage XR®.

Keywords: Metformin Hydrochloride, Flow-through cell, Immediate release, Controlled release

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INTRODUCTION

For many years, efforts have been made to minimize the number of *in vivo* studies required to approve a new molecule or a generic product. One of the approaches currently used is the *in vitro* (mainly dissolution) tests that act as a tool to predict drug product performance *in vivo* [1-4]. It is necessary to have precise and reproducible dissolution data resulting from physiochemically and hydrodynamically determined conditions to compare variability and reproducibility for *in vitro* dissolution data and to manage using such results as a replacement for *in vivo* bioavailability, bioequivalence testing and *in vitro*/*in vivo* correlations (*IVIVC*) [5].

Dissolution testing is empirical *in vitro* laboratory performance test that judges how a drug is released from its dosage form efficiently. During drug development, dissolution profiles have been utilized to comprehend the influence of formulation composition on the *in vitro* release of an active pharmaceutical ingredient (API). It plays as well an important role in the context of science and risk-based process development, validation and evaluation of post-approval formulation changes to drug product quality [6].

Also, after product development, *in vitro* dissolution is an important test in QC to ensure batch to batch consistency, to establish shelf life during stability studies [7] and to predict *in vivo* performance (i.e. bioavailability) [2].

Although the Flow through the cell (FTC) became an official USP method since 1995 (USP Apparatus IV) [8], *in vitro* dissolution studies using this apparatus under different operational conditions and/or features are few in literature [5, 9-17]. Our previous studies using the FTC proved that we should optimize the *in vitro* dissolution conditions for the finished product or during the preparation of different formulations to achieve accurate and reproducible results and to detect the effect of minor formulation changes upon storage [18].

Metformin, 1,1-dimethyl biguanide, has properties of a strong base (pKa, 11.5) (log P, −1.43). Metformin hydrochloride (MH) is a salt of a strong base and a strong acid so it is completely ionized in the physiological pH [19]. MH is considered the first-line treatment according to international guidelines for patients with (T2DM). It belongs to a class of drugs known as the biguanides. Bioavailability of MH, when given orally, is 50–60% and it's the biological half-life of is 1.5–4.5 h and its main site of absorption is proximal small intestine. Chemically, MH is freely soluble in water and is classified as class III according to the Biopharmaceutical Classification System (BCS) with high solubility and low permeability [20-23].

Currently, MH is available in the market as immediate-release (IR) and controlled release (CR) dosage forms. Glucophage® is the innovator product that stands out in terms of quality and efficacy, but because of the high price associated with some branded products, some patients and governments may be biased to go for generic products [24]. Although the active ingredient is synonymous in both generic and brand name drug, evidence proves that there are definite differences in their therapeutic effects [25]. This may be due to differences in rate and extent of absorption [26], excipients and manufacturing processes [27] or the manufacturing variables such as the mixing effect and granulation procedure [7]. Few studies compared the performance of innovator and generic products of MH in different countries [26, 28-35].

Till now, there are 13 dissolution methods in the U. S. Pharmacopeia [36] for MH tablets to describe its release profile utilizing either apparatus I or apparatus II at 100 rpm and 1000 ml of phosphate buffer solution (pH 6.8) as dissolution medium. Nevertheless, it is still valuable to investigate the *in vitro* dissolution performance of MH tablets employing USP apparatus IV versus USP apparatus II based on its numerous merits.

Therefore, the focus of this study was to evaluate an *in vitro* dissolution method for MH, using the flow-through cell apparatus

(USP apparatus IV) and beaker method (non-official method simulating the USP paddle method) compared to the pharmacopeial USP apparatus II method. This will be carried out on MH tablet products available in the Egyptian and European market.

MATERIALS AND METHODS

Materials

Pure metformin hydrochloride (MH) was kindly donated from Sigma, Cairo, Egypt. MH products evaluated were immediate and controlled release tablets (850 mg or 1000 mg MH/tablet) purchased from the Egyptian and European markets. All tests were performed within the products expiration date.

Investigated IR products were: two reference products with the same trade namely: R1-Glucophage® 850 mg tablets, Merk Serono, France (purchased from a retail pharmacy in Cairo, Egypt) (batch number 110017); R2-Glucophage® 850 mg tablets, Merk Serono, France (purchased from country representative) (LOT number F5503). Two generic products: G1-Cidophage® 1000 mg tablets, CID, Egypt (batch number 01140534); G2-Metformin arrow® 1000 mg tablets, Arrow Generiques, France (LOT number 1297).

Investigated CR products: reference product; R3-Glucophage XR® 1000 mg tablets, Merk serono, Germany (purchased from a retail pharmacy in Cairo, Egypt) (batch number 171521) and Generic product; G3-Cidophage Retard® 850 mg tablets, CID, Egypt (batch number 03140848).

Sodium hydroxide pellets and Potassium dihydrogen ortho-phosphate were purchased from ADWIC, Egypt. Methanol (HPLC grade, TEDIA, USA) was used for stock solution preparation. Milli-RO purified water (Millipore Corp., Billerica, MA, USA) was used to prepare the dissolution medium.

Methods

Analysis of MH

A standard curve ranging from 0.5 to 10 µg/ml in phosphate buffer (pH 6.8) was constructed. A stock solution was prepared by dissolving 5 mg of MH powder in 50 ml methanol to yield a concentration of 100 µg/ml. This solution was serially diluted with phosphate buffer (pH 6.8) to yield the desired concentration range. The absorbance of the prepared solutions was measured spectrophotometrically (DU–650 UV-Vis spectrophotometer, Beckman, USA) at predetermined λ_{max} of 231 nm against the phosphate buffer (pH 6.8) as blank. Absorbance was plotted against MH concentration and the response factor was calculated. Each concentration was analyzed in triplicate and the mean values were calculated. A linear zero-intercept relationship was established, where the slope and regression coefficient were 0.1026 and 1, respectively. Percent recoveries ranged from 94.02% to 100.37%, and the average response factor was 9.865±0.254.

Tablet characteristics

Uniformity of weight

Twenty tablets of each MH product were weighed individually and the weight variation was calculated using Microsoft Excel 2010.

Physical parameters

Tablet Hardness Tester [MT 50 3 in 1 Hardness, Diameter and Thickness Tester (Sotax-MT 50 MultiTest 50, Switzerland)] was used for determination of tablet dimensions and hardness of the tested brands (mean of twenty tablets for each product was calculated).

Content uniformity

Twenty tablets of each product were weighed, ground and the weight equivalent to one tablet was transferred quantitatively into 100 ml volumetric flask. About 70 ml of water was added to each flask and then shaked for 15 min using "temperature-controlled shaking water-bath" (Lab-Line, USA) at 37 °C. The final volume was adjusted with water followed by mixing. The solution was then filtered and appropriate dilutions were done to the filtrate using water. The absorbance was then measured spectrophotometrically (UV-Visible spectrophotometer, Beckman, DU-650, USA) at the predetermined λ_{max} at 231 nm for MH [37].

Comparative *in vitro* dissolution study of MH products

USP apparatus II (pharmacopeial method)

For such studies, MH products were examined utilizing USP apparatus II (AT8-Xtend, Sotax, Switzerland) at a rotational speed of 100 rpm at 37.0±0.5 °C in 900 ml phosphate buffer (pH 6.8) (fig. 1A). Each dissolution study was done on six tablets. Samples were drawn manually. Each sample was replaced with an equal amount of blank buffer at 37 °C. Samples were then filtered through a syringe filter with a pore size of 0.45 µm and a diameter of 25 mm. Dissolution samples were analyzed spectrophotometrically (DU–650 UV-Vis spectrophotometer, Beckman, USA) at predetermined λ_{max} of 231 nm against the blank.

Flow-through cell apparatus (USP apparatus IV)

The comparative in vitro dissolution studies of marketed MH products, were carried out using the closed-loop setup of FTC [USP Apparatus IV, a Dissotest CE-6 equipped with a CY 7-50 piston pump (Sotax, Switzerland)]. Each tablet was placed into the large dissolution cell (22.6 mm diameter). A built-in filtration system with 0.7-µm Whatman glass micro-fiber (GF/F and GF/D) and glass wool were used throughout the study (fig. 1B). The dissolution medium was filtered degassed phosphate buffer (pH 6.8) maintained at 37.0±0.5 °C and pumped at 8±0.2 ml/min. The dissolution studies were carried out on six tablets. Sample fractions were collected at the following time intervals: 5, 10, 15, 20, 25, 30, 45, 60 and 75 min for IR products and for appropriate fractions for up to 6 h for CR products. The fractions were analyzed by UV/spectrophotometric method at 231 nm against phosphate buffer (pH 6.8) as blank.

Beaker method

For the beaker method, the set up consisted of 1L jacketed beakers connected to refrigerated circulator apparatus (julabo circulators F10-VC, Germany). Each beaker was filled with 900 ml phosphate buffer (pH 6.8) maintained at 37.0±0.5 °C. A constant stirring rate was maintained in each beaker using a magnetic stirrer with the magnet kept below a stainless steel mesh (fixed height = 1.5 cm) placed at the bottom of each beaker (fig. 1C). Samples fractions were collected at specified time intervals for a total of 75 min for IR products and 6 h for CR products. The amount dissolved of MH was determined spectrophotometrically as described previously. All experiments were done on six tablets.

Statistical analysis of *in vitro* dissolution data

Similarity factor (f_2)

The dissolution profiles of different MH IR and CR market products were compared with the reference product in different apparatuses using similarity factor (f_2) as proposed by Moore and Flanner [38] which is defined as follows (Equation 1):

$$f_2 = 50 \log\left\{\left[1 + \left({}^{1}/_{n}\right)\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad \text{Equation (1)}$$

Where R_t is the percentage of released drug for a reference batch at time point t, T_t is the percentage of released drug for the test batch, n is the number of pull points collected during the *in vitro* release test, R_t and T_t are the cumulative percentages release at the selected time point of the two tested formulae. FDA has set a public standard of f_2 value of 50-100 to indicate similarity between two dissolution profiles [39].

Dissolution efficiency

Khan and Rhodes [40] used the trapezoidal rule to calculate the area under the dissolution curve at the time (t) to obtain the dissolution efficiency (D. E.) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [41]. (D. E.) is defined as follows:

$$D.E = \frac{\int_0^t ydt}{y_{100} \times t} \times 100 \quad \text{Equation (2)}$$

RESULTS AND DISCUSSION

All MH tablets of the six products under investigation showed acceptable tablet characteristics regarding weight variation, physical parameters and content uniformity, as shown in table 1.

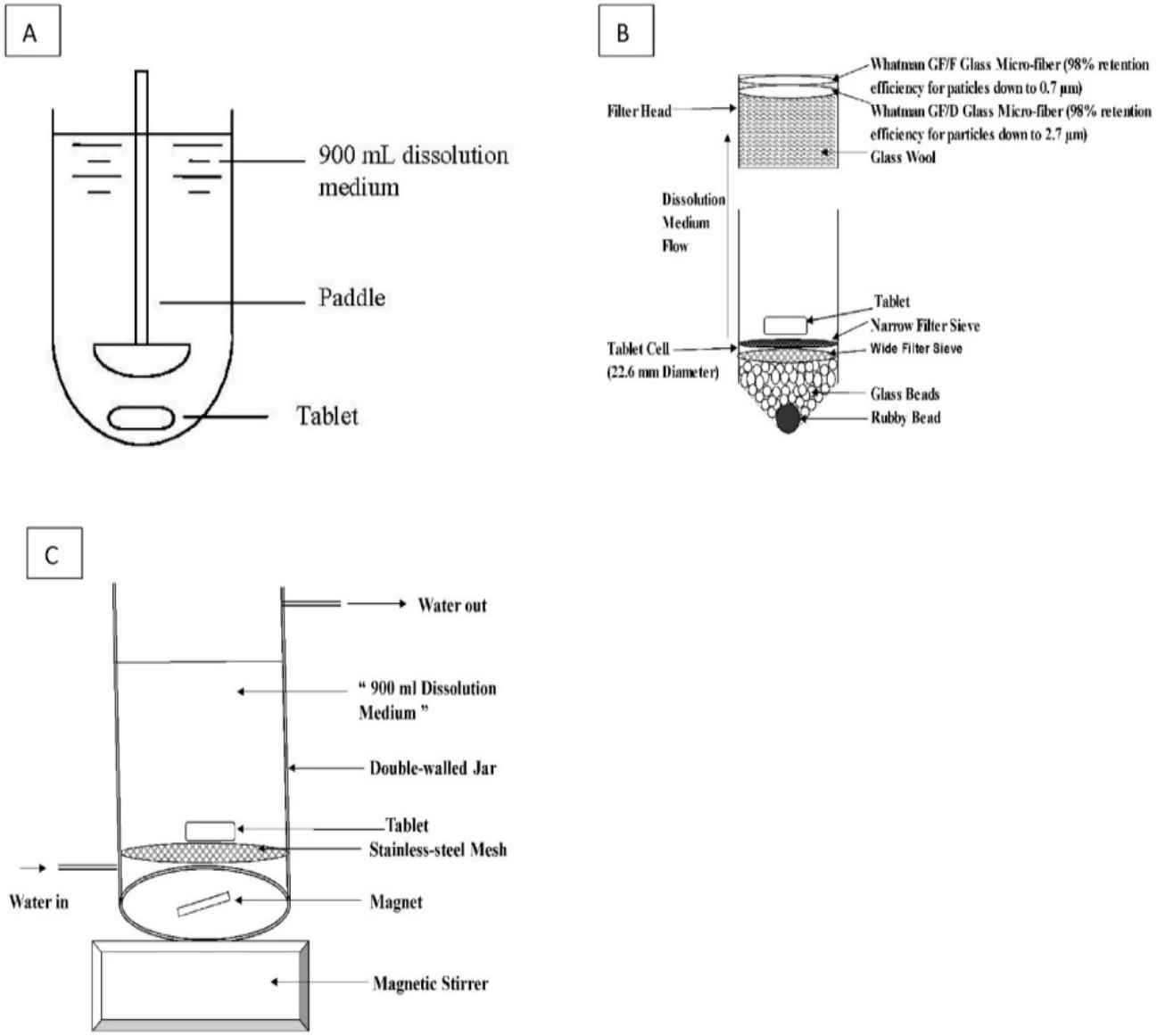

Fig. 1: Schematic diagrams of: (A) USP apparatus II, (B) USP apparatus IV, (C) Beaker method

Table 1: Evaluated physicochemical properties of the six MH market products

Tested product	Appearance	Average weight (mg)	Hardness (N)	Width (mm)	Length (mm)	Thickness (mm)	Diameter (mm)	Drug Content (%)
Glucophage® 850mg, Egyptian market (R1).	Round	904±6.6	320±13.8			6.5± 0.01	13.5± 0.02	98.4± 0.5
Glucophage® 850mg, French market (R2).	Round	901±6.1	281±4.1			6.5± 0.1	13.5± 0.01	99.9± 0.4
Cidophage® 1000 mg	Oblong	1071±8.2	628±15.1	9± 0.2	20±0.1	6.32± 0.2		98.6± 1
Metformin arrow® 1000 mg (G2).	Oblong	1108±3.6	443±17.6	8.7±0.01	21.9±0.2	7.3±0.01		95.4± 0.6
Glucophage XR® 1000 mg (R3).	Oblong	1441±8.8	141±3.7	10.6± 0.1	22.12±0.01	8.2± 0.1		95± 0.4
Cidophage Retard® 850 mg (G3).	Round	899±7.8	182±16.8			6.4± 0.02	13.4± 0.01	95.3± 2

*P. C: Product Code, L. N: Lot Number, **All values expressed as mean±SD, where n=20

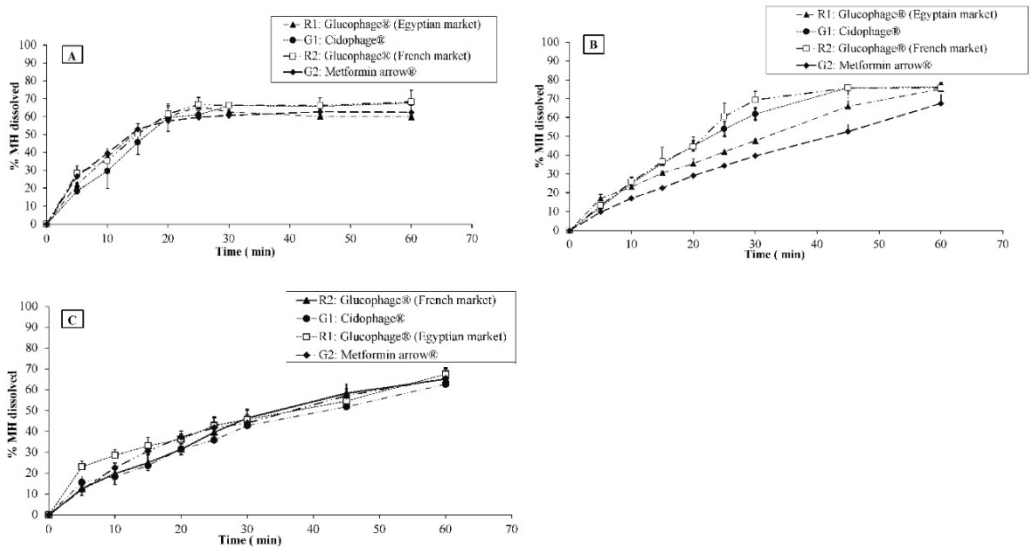

Fig. 2: Dissolution profiles of four MH IR products obtained using: (A) USP apparatus II, (B) USP apparatus IV, and (C) Beaker method (mean±SD, n = 3)

Comparative *in vitro* dissolution study of MH IR products

The results of the dissolution experiments carried out in USP apparatuses II, IV and the beaker are presented in (fig. 2: A-C). In the case of USP apparatus II and beaker method, the dissolution behavior of generic products G1 and G2 compared with reference products R1 and R2 were almost identical. On the other hand, dissolution differences were detected upon applying USP Apparatus IV.

The calculated f_2 values are presented in fig. 3 to compare MH dissolution profiles of R2, G1 and G2 versus R1: Glucophage® 850 mg (Egyptian market). D. E. was also calculated, table 2 lists the corresponding results obtained for the difference of the mean D. E. (D. D. E.) and the difference in confidence intervals (D. C. I.). If the differences of the mean D. E. and the 95% C. I. are within limits (±10%), it can be concluded that the dissolution profiles of the reference and test are equivalent [41].

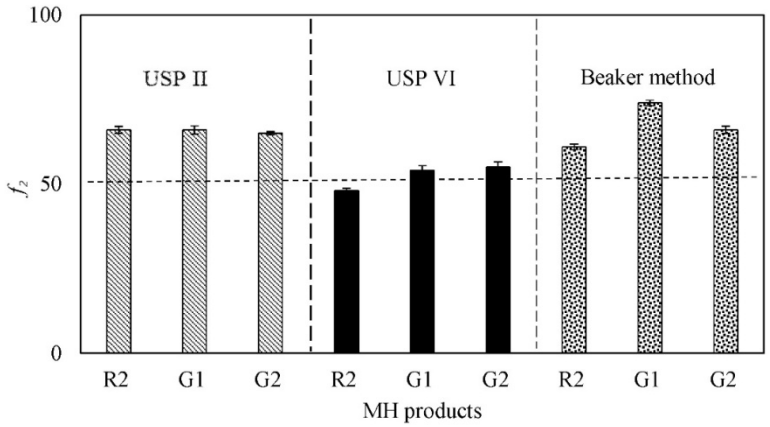

Fig. 3: Comparison between dissolution profiles of different MH IR market products (R2, G1, G2) versus R1 (Glucophage®) expressed by the similarity factor "f_2", utilizing different apparatuses (mean±SD, n = 3)

USP apparatus II

The dissolution profiles of R2, G1 and G2 were compared to that of the innovator product R1. It was found that the two parameters of D. E. (D. D. E. and D. C. I.) were accepted for R2: Glucophage® 850 mg (French market), but for the generics Cidophage® (G1) and Metformin arrow® (G2), D. C. I. was out of range. Thereby, the two products named Glucophage® (R1 and R2) had a similar dissolution profile in terms of D. C. I., D. D. E. (table 2) and f_2 (fig. 3), while G1 and G2 declared dissimilar dissolution profiles when compared to R1 only in terms of D. C. I. Meanwhile, they all revealed similar dissolution profiles in terms of f_2 (fig. 3) and D. D. E (table 2). The $Q_{30\ min}$ values were 66.3%, 62.7%, 66.2% and 58.7% for R1, R2, G1, and G2, respectively. Thus, we can conclude that USP apparatus II could hardly detect differences in dissolution profiles of the tested MH IR products.

Table 2: Mean dissolution efficiencies (D. E.) with 95% confidence intervals (C. I.) calculated from *in vitro* release data of MH IR tablets

Apparatus	Tested product	Product code	Mean D. E. (%) with C. I.	D. D. E.	D. C. I.
USP II	Glucophage® 850 mg, Egyptian market	R1	54.65 (50.84, 58.46)	0	0
	Glucophage® 850 mg, French market	R2	58.85 (54.21, 63.48)	-4.2	4.25
	Cidophage® 1000 mg	G1	55.09 (48.72,61.45)	-0.44	9.74

	Metformin arrow® 1000 mg	G2	55.84 (51.33, 60.35)	-1.19	7.13
USP IV	Glucophage® 850 mg, Egyptian market	R1	51.76 (45,65.52)	0	0
	Glucophage® 850 mg, French market	R2	57.62 (49.22,66.02)	-5.86	16.3
	Cidophage® 1000 mg	G1	57.86 (54.73,60.99)	-6.1	10.79
	Metformin arrow® 1000 mg	G2	44 (17.66, 70.39)	7.76	47.86
Beaker method	Glucophage® 850 mg, Egyptian market	R1	46.47 (40.56, 52.38)	0	0
	Glucophage® 850 mg, French market	R2	48.74 (41.63, 55.85)	-2.27	10.75
	Cidophage® 1000 mg	G1	43.92 (43.75, 44.10)	2.55	8.63
	Metformin arrow® 1000 mg	G2	49.56 (43.65, 55.47)	-3.09	8.73

*D. E.: Dissolution Efficiency, C. I.: Confidence Intervals, D. D. E.: Difference of the mean D. E. between the innovator and the tested product, D. C. I.: Difference in confidence intervals and is calculated by considering the maximum possible mean D. E. value of Innovator and minimum possible mean D. E. value of other products (mean±SD, n = 3).

Other researchers studied the commercially available MH IR products using USP apparatus II. Olusola *et al.* [28] compared the dissolution rate of eight commercially available MH tablets in Nigeria and found that only four brands could be considered as bio-pharmaceutically and chemically equivalent. Sougi *et al.* [34] conducted a study for evaluation of fifteen MH IR commercial brands in Ghana and concluded that not all the commercial brands of MH tablets had similar dissolution profiles as the innovator depending on the f_2 analysis. Previously, a study done by Hamdan and Jaber [42] on five brands of MH in Jordanian market declared that four out of five brands were not equivalent to innovator brand except for one that is equivalent to an innovator in terms of f_2 analysis of the dissolution profiles. Moreover, another study was done on five IR brands of MH in the Saudian market, which also revealed that all the brands, except one, were non-equivalent to innovator Glucophage product [33].

USP apparatus IV

Dissolution performance of MH IR products in USP apparatus IV is illustrated in fig. 2(B). The $Q_{30\ min}$ results were 47.6%, 69.3%, 61.8% and 40% for R1, R2, G1, and G2, respectively. Fig. 2 clarified that USP apparatus IV was the dissolution apparatus that revealed the highest sensitivity and discriminative capability in differentiating between the dissolution behavior of MH products than USP apparatus II and beaker method. Similar observations were reported by Hurtado y de la Peña *et al.* [43] who highlighted by statistical analysis the discriminative capability of USP apparatus IV versus USP apparatus II in differentiating the release characteristics of tested albendazole products.

Fig. 3 shows a comparison between dissolution profiles of different MH IR market products (R2, G1, G2) versus R1 (Glucophage®) expressed by similarity factor "f_2", utilizing different apparatuses while table 2 shows the mean dissolution efficiencies (D. E.) with 95% confidence intervals (C. I.) calculated from *in vitro* release data of MH IR tablets. According to fig. 3 and table 2, USP apparatus IV revealed that the two innovator products (R1 and R2), named Glucophage, (from Egyptian and French markets) have dissimilar dissolution profiles in terms of f_2 (48), D. D. E. (-5.86) and D. C. I. (16.3±10%).

The dissolution profiles of the two generic MH IR products (G1, G2) were compared with the innovator R1 using f_2 (fig. 3) and D. E. (table 2). f_2 values were 54 and 55 for G1 and G2, respectively indicating similar dissolution profiles (fig. 3). However, upon comparing the dissolution efficiency of these two generic MH products with respect to the innovator R1, it was found that D. D. E values (-6.1 and 7.76 for G1 and G2, respectively) and D. C. I. values (10.79 and 47.86 for G1and G2, respectively) were out of range (table 2) which indicated dissolution dissimilarity between G1 and G2 versus innovator R1 under these operational conditions.

In case of R1 and R2, our results that show dissolution dissimilarity is in consistence with Stuart *et al.* [31] who assumed that the two MH innovator products having similar trade name (Glucophage), but came from different manufacturers, were statistically different regarding their dissolution profiles. Likewise, Crison *et al.* [44] stated that MH IR tablets obtained from different markets showed diverse drug release profiles. Moreover, in a previous study done using USP apparatus IV [12], the authors concluded that two tested reference products of diclofenac sodium tablets (Voltaren 100 mg) manufactured in different manufacturing sites (Novartis-Egypt, Novartis-Switzerland), displayed notable differences in the release rate of diclofenac sodium. In this respect, the two products might give different *in vivo* data [45].

The perceived variations between results obtained from USP apparatus II and IV can be explained due to differences in the hydrodynamic conditions that characterize this system. Medina *et al.* [46] reported a comparative *in vitro* dissolution study of carbamazepine immediate-release products using the USP apparatus II method and the flow-through cell apparatus and concluded that all products showed a slower dissolution rate in USP apparatus IV than the one found with the USP paddle method. Langenbucher *et al.* [48] clarified that kind of behavior to be related to the hydrodynamic conditions that illustrate the flow-through cell apparatus, where no agitation mechanisms exist so the dosage form is exposed to a uniform flow, like the surroundings of the GIT, producing different dissolution pattern.

The hypothesis of the effect of variable hydrodynamics on drug dissolution came to be verified by McCarthy *et al.* [49] depending on a high-performance computing software system to simulate the USP dissolution apparatus II (paddle apparatus) to characterize the fluid hydrodynamics in the method. Similarly, Computational analysis was used to examine the hydrodynamic environment within USP apparatus II at common operating conditions by Kukura *et al.* Their results showed that the uneven distribution of hydrodynamic forces in USP apparatus II is a direct cause of dissolution testing variability [50].

Beaker method

The dissolution profiles of the four MH IR tested products obtained using the beaker method are plotted in fig. 2(C). R1, R2, and G1 apparently showed slower dissolution rates in beaker method than in other apparatuses in terms of Q30 min; the values were 46.7%, 45.8%, 42.8% for R1, R2 and G1, respectively. But for G2, Q30 min (44%) was close to that of USP apparatus IV (40%). In terms of f2 (fig. 3) and D.D.E. (table 2), R2 and the generic products (G1 & G2) had similar dissolution profiles with respect to innovator product R1, opposing D.C.I. values which revealed dissimilar dissolution profiles (table 2).

From the previous results, it was found that the dissolution profiles of the two investigated MH IR innovator products (R1 and R2) were similar when USP apparatus II (f_2 = 66) and beaker method (f_2 = 61) were used, while opposite results were found with USP apparatus IV (f_2 = 48) (fig. 3). Nevertheless, Wong and Ngo [32] reported that even if multiple generic MH IR tablets had different dissolution profiles *in vitro*, the *in vivo* performance might not likely be diverted to a clinically significant extent. The previous conclusion was in complete accordance with Oyetunde *et al.* [29] who discussed in their study that even if the dissolution performance of BSC class III drug products were found to be relatively slow, they may still have similar *in vivo* absorption.

Our study revealed that the reported MH pharmacopeial dissolution test was not discriminating enough, to show minor differences between dissolution patterns of different generics (fig. 3). On the other hand, USP apparatus IV was more beneficial in the

development of a much more discriminating dissolution method than the pharmacopeial method, similar observations were stated by Medina *et al.* [46] who studied *in vitro* dissolution profiles of carbamazepine IR generic tablet products using different dissolution apparatuses (II and IV). In a recent study, similar observation regarding USP apparatus IV and II was noticed for marketed suspensions of carbamazepine [47]. Again this was in accordance with the work done by Gite *et al.* [51] on atorvastatin using USP apparatus I and IV.

According to USP specifications, the percent of MH dissolved from IR tablet products should not be less than 75% of the labeled amount of MH in 30 min ($Q_{30\ min}$). It is noticeable from $Q_{30\ min}$ values listed above that no matter which apparatus was employed, none of MH IR products met the requirements of the USP pharmacopeia [37]. Likewise, other researchers faced such out of limits results. For example, Hurtado y de la Peña *et al.* [43] reported that for different marketed albendazole products, only the reference product and one of the generic products studied met the USP specifications. Moreover, Emara *et al.* [18] presented two commercial products of gliclazide that failed to meet the requirements described by the British Pharmacopoeia.

Comparative *in vitro* release study of MH CR products

Dissolution profiles of the two MH CR products studied, R3 and G3, obtained using USP apparatus II, USP apparatus IV and beaker method are shown in fig. 4 (A-C). Regarding MH CR products, the amount of drug released in 6 h (Q_{6h}) according to USP specifications for MH tablet assay should be between 65-85% of the labeled amount of MH [36]. The dissolution results of MH CR commercial products (fig. 4: A-C) revealed that the innovator product R3 (Glucophage XR®) did not meet these USP release criteria. Q_{6h} values for R3 were 40.1%, 37.8% and 57.7% obtained by USP apparatuses II, IV and beaker method, respectively. On the other hand, the generic product G3 (Cidophage Retard®) complied with these specifications.

Fig. 5 displayed a comparison between dissolution profiles of MH CR generic product G3 (Cidophage Retard) versus R3 (Glucophage XR®) expressed by the similarity factor "f_2", utilizing different apparatuses. Meanwhile, table 3 listed the mean dissolution efficiencies (D. E.) with 95% confidence intervals (C. I.) calculated from *in vitro* release data of MH CR tablets. For all studied apparatuses, the dissolution profile of the generic product G3 (Cidophage Retard®) was dissimilar with the innovator R3 in terms of D. D. E., D. C. I. and f_2 (table 3 and fig. 5). Thereby, it might not be interchangeable with the reference brand. This variability in MH release may be due to differences in particle size and/or surface area of MH particles, uneven distribution of hydrodynamic force [50] or differences in the method of manufacturing, compression force or machinery [52].

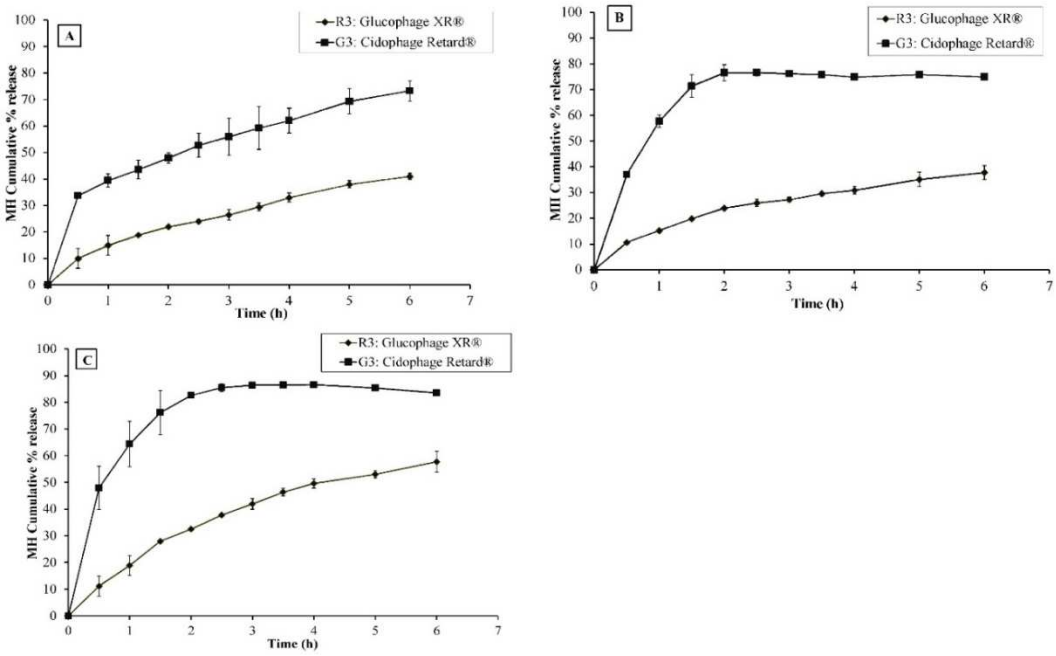

Fig. 4: Dissolution profiles of two MH CR products obtained using: (A) USP apparatus II, (B) USP apparatus IV, and (C) Beaker method (mean±SD, n=3)

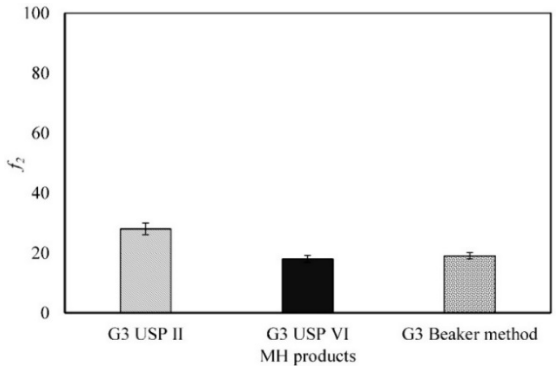

Fig. 5: Comparison between dissolution profiles of G3 generic product (Cidophage Retard) versus R3 (Glucophage XR®) expressed by the similarity factor "f_2", utilizing different apparatuses (mean±SD, n = 3)

Table 3: Mean dissolution efficiencies (D. E.) with 95% confidence intervals (C. I.) calculated from *in vitro* release data of MH CR tablets

Apparatus	Tested product	Product code	Mean D. E. (%) with C. I.	D. D. E.	D. C. I.
USP 2	Glucophage XR® 1000 mg	R3	27.27 (22.92,31.61)	0	0
	Cidophage Retard® 850 mg	G3	53.04 (50.42,55.67)	-25.77	-18.81
USP 4	Glucophage XR® 1000 mg	R3	25.57 (14.86, 36.28)	0	0
	Cidophage Retard® 850 mg	G3	67.57 (64.27, 70.87)	-42	-27.99
Beaker method	Glucophage XR® 1000 mg	R3	37.63 (21.55,53.72)	0	0
	Cidophage Retard® 850 mg	G3	75.45 (55.66,95.25)	-37.82	-1.94

*D. E.: Dissolution Efficiency, C. I.: Confidence Intervals, D. D. E.: Difference of the mean D. E. between the innovator and the tested product, D. C. I.: Difference in confidence intervals and is calculated by considering the maximum possible mean D. E. value of Innovator and minimum possible mean D. E. value of other products (mean±SD, n = 3).

Despite the possible importance of the effect of different excipients on the release profile of MH tablets under test, it could not be evaluated because only the innovator product R3 (Glucophage XR®) listed the excipients on its pamphlet. In this context, Block *et al.* and Stuart *et al.* [31, 53] stated that the difference in dissolution profiles of products could be attributed to the excipients and/or the manufacturing process. Furthermore, Berthelsen *et al.* [54] reported that excipients might disturb the drug-filter interaction/adsorption in USP apparatus IV, causing differences in dissolution profiles and interfering with the prediction of *in vivo* data.

Shaw and Krauss [55] informed that the FDA has not publicized safety in generic-to-generic switches, which could possibly cause drug concentration deviations up to 40%. Our present study involving USP apparatus II and IV and beaker method revealed significant differences in the rate of release of MH from Egyptian CR generic product investigated as compared to the innovator product.

Although USP apparatus IV can usually discriminate between different pharmaceutical products, nevertheless, it has some disadvantages as there is always a risk of filter clogging, difficulties in confirming the flow rate during testing, and a necessity for a very large amount of dissolution medium for open system runs [54]. As a result of such possible problems, it might still be better to use the Pharmacopeial method (USP apparatus II).

CONCLUSION

Data with the flow-through cell apparatus approve that the dissolution method proposed has a greater discriminating ability compared to USP apparatus II and beaker method to assess differences in dissolution profiles of MH market products. Our results revealed that the same trade name does not consequently indicate that products are pharmaceutically identical. The study showed that the dissolution performance of the investigated MH market products was questionable, where only the generic CR product succeeded to meet the USP dissolution specifications under the studied test conditions. On the contrary of MH IR products, generic MH CR product showed dissimilar dissolution behavior compared to the innovator product. Accordingly, we recommend that physicians and pharmacists should generally avoid the hypothesis that generic and reference market products are therapeutically equivalent and hence could be interchangeable safely, even when labeled to contain the same drug substance. It is possible to mention that MH products with differences in dissolution performance are candidates to show bioavailability differences.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally to this manuscript

CONFLICT OF INTERESTS

There is no conflict of interest to disclose

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