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Comparison of Dissolution Profiles and Apparent Permeabilities of Commercially Available Metformin Hydrochloride Tablets in Turkey

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ABSTRACT

The purpose of this study was to evaluate the similarity of dissolution and permeability properties of commercially available immediate-release metformin hydrochloride (MH) tablets (1000 mg strength) including five generic products obtained from the Turkish drug market (tablets A–E) and two reference products (obtained from the Turkish and European markets). In vitro dissolution studies were conducted in accordance with the MH tablet monograph in the USP (1000 mL, 75 rpm) and with the BCS-based biowaiver guidance in three different media (pH 1.2, pH 4.5, and pH 6.8; 900 mL, 50 rpm). The apparent permeability of MH in all tablets and raw MH was determined in Caco-2 cells. Dissolution studies revealed that neither the generics (except generic tablet B) nor the reference tablets fulfilled the criteria for very rapid dissolution. Although the dissolution profiles of the reference tablets were similar ($f_2 > 50$), none of the generic tablets were similar to either of the reference tablets. Permeability of MH for all reference and generic tablet formulations was similar to that of raw MH ($p > 0.05$). In contrast, a significant difference in permeability was observed between the two reference tablets ($p < 0.05$), and only one generic tablet (A) had permeability similar to both reference tablets. As MH has low permeability, potential alterations in permeability due to the dosage form can affect its bioavailability. The results of this study indicate that immediate-release MH tablets do not meet the criteria for very rapid dissolution for the BCS-based biowaiver.

KEYWORDS: Metformin hydrochloride, dissolution profile, biowaiver, permeability

INTRODUCTION

Metformin hydrochloride (MH) is a biguanide antidiabetic agent used for the treatment of type 2 diabetes mellitus (*1, 2*). It is the most frequently used oral antidiabetic agent, used by approximately 150 million patients per year worldwide in the last 60 years. MH is safe and effective (*3*), and is recommended as the first-line medication by the American Diabetes Association and European Association for the Study of Diabetes (*4*). The reference MH tablets for standard care are available in the market in three strengths (500, 850, and 1000 mg) (*5*). In addition to the reference MH tablets, six generic formulations of the same strengths are commercially available in the Turkish Drug Market.

According to the European Medicines Agency (EMA), United States Food and Drug Administration (FDA), and World Health Organization (WHO) guidelines, immediate-release (IR) MH-containing tablets are subject to a BCS-based biowaiver because MH drug substance is a BCS Class 3 drug (*6–10*). The criteria for the BCS-based biowaiver recommended by EMA and FDA are as follows: high solubility and limited absorption for drug substance; very rapid in vitro dissolution rate for test and reference drug products; and no change in excipients that might affect bioavailability (*7, 8*).

Two main parameters govern the oral absorption of compounds, namely the dissolution from the dosage form and permeability across the gastrointestinal tract. For BCS Class 1 compounds, neither dissolution nor permeability are expected to limit the absorption as the compounds have high solubility and high permeability. In contrast, the rate-limiting step in absorption is dissolution for Class 2 compounds and permeability for Class 3 compounds. According to the EMA, "a generic medicinal product is a product which has the same qualitative

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and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies" (*7*). Therefore, a BCS-based biowaiver may be applicable for IR products of Class 1 and 3 compounds if all recommended conditions are met (*7, 8*).

The dissolution test is an important tool in drug development and quality control studies for tablet formulations. It is also used to design new formulations, develop in vitro-in vivo correlations, control in-process and finished product specifications, show the similarity of pharmaceutical dosage forms, and evaluate the bioequivalence of reference and generic products (*11, 12*). Permeability is the rate-limiting step in the oral absorption of BCS Class 3 compounds such as MH (*13*). The permeability of a drug substance can be investigated by in vitro methods (monolayers of suitable epithelial cells and excised intestinal tissues), in situ, through in vivo intestinal perfusion in a suitable animal model, and in vivo in human studies (absolute bioavailability and mass balance studies) (*8*). The Caco-2 monolayer cell model is used widely as an in vitro method to study the transport of soluble drugs. However, owing to the absence of M cells, the uptake studies of particles are not possible. Therefore, various co-culture models have been established to emphasize the human intestine with M-cell like morphology. Kerneís et al. developed co-cultures of Caco-2 cells and Peyer's patch lymphocytes in which the murine lymphocytes were replaced with the human B-cell line Raji. Gullberg et al. also established physically separated co-cultures of human Raji B-and Caco-2 cells as a simpler phenotypic model to be used for oral drug delivery systems, such as oral vaccine delivery (*14–16*).

Among these methods, permeability across Caco-2 cells is a useful in vitro tool for investigating the apparent permeability of active ingredients and the potential effects of excipients on their permeability. The Caco-2 monolayer shows higher transepithelial electrical resistance (TEER) values than another human colon adenocarcinoma cell line HT29; thus, it provides a better simulation of in vivo conditions (*17*). Caco-2 cells express transporters, enzymes (e.g., esterase), and receptors that are expressed in the epithelium (*18*); however, because of a potentially low (or absent) expression of efflux and uptake transporters, its use in BCS classification is limited to passively absorbed drugs. Although there is no mucus and unstirred water layer in Caco-2 cells, a good correlation was observed between Caco-2 and the jejunum with regard to passive drug absorption (*19–21*). In 2018, the draft ICH guideline M9, on Biopharmaceutics Classification System-based biowaivers (step 2), revealed a validated and standardized in vitro permeability assessment method in Caco-2 cells (*22*). Some regulatory authorities (e.g., South Korea, USA) accept Caco-2 cell data as primary evidence of permeability; others (e.g., Australia, Canada, EU, New Zealand, WHO) consider it as supporting data (*23*).

The purpose of this study was to investigate the similarity of five generic MH tablets (1000 mg strength) available in the Turkish drug market to the reference MH tablets obtained from Turkish and European Markets through an evaluation of their dissolution and permeability. Dissolution studies were performed in accordance with the MH tablet monograph in the USP and the BCS-based biowaiver guidance in three different medium conditions (pH 1.2, pH 4.5, and pH 6.8). Permeability studies across the Caco-2 cell monolayer were conducted to determine the permeability of raw MH and MH in commercial tablets.

MATERIALS AND METHODS

Materials

MH was kindly provided by Sanovel Pharmaceuticals, Turkey. HPLC-grade acetonitrile was obtained from Sigma-Aldrich. Water was purified by using a Milli-Q system (MilliporeUSA). Potassium chloride (≥ 99.0%; Sigma-Aldrich, USA), hydrochloric acid (36.5%–38.0%; J.T. Baker, Holland), sodium acetate trihydrate (≥ 99.0%; Sigma-Aldrich, St. Louis, MO, USA), acetic acid (99.5%–101.5%; Carlo Erba, Italy), monobasic potassium phosphate (≥ 99%: Sigma-Aldrich, St. Louis, MO USA), and sodium hydroxide (≥ 97%; Merck, Germany) were used as received. Caco-2 cells (a human colon carcinoma cell line) were purchased from American Type Culture Collection (ATCC, Gaithersburg, MD, USA). Dulbecco's Modified Eagle's Medium (DMEM), Hank's balanced salt solution (HBSS), and fetal bovine serum (FBS) were all purchased from Biochrom AG (Berlin, Germany), penicillin-streptomycin solution was obtained from Life Technologies, Inc. (Carlsbad, CA, USA), and Thincerts cell culture inserts (0.4 µm) were obtained from Greiner Bio-One (Frickenhausen, Germany). All other chemicals were of analytical grade.

Tablet Samples

Commercial tablets containing 1000 mg MH were obtained from local pharmacies in Turkey and Europe (Switzerland). The generic tablets obtained from Turkey were labeled randomly as A, B, C, D, and E. The reference

Table 1. Excipient Contents of Generic and Reference Tablets Containing 1000 mg MH

Function	A	B	C	D	E	TR	ER
Hydrophilic Polymer	Hydroxy propyl methyl cellulose		Hydroxy propyl methyl cellulose	Hydroxy propyl methyl cellulose	Hydroxy propyl methyl cellulose	Hydroxy propyl methyl cellulose	Hydroxy propyl methyl cellulose
Plasticizer	Polyethylene glycol 6000		Polyethylene glycol Propylene glycol	Polyethylene glycol 4000	Polyethylene glycol 4000	Polyethylene glycol 400 Polyethylene glycol 8000	Polyethylene glycol 400 Polyethylene glycol 8000
Binder, Disintegrant	Povidone K25	Povidone K30		Copovidone	Povidone K9	Povidone K30	Povidone K30
Diluent, Disintegrant		Microcrystalline cellulose		Microcrystalline cellulose Sodium starch glycolate Lactose monohydrate			
Lubricant	Magnesium stearate	Magnesium stearate	Magnesium stearate Talc	Magnesium stearate Colloidal silicon dioxide	Magnesium stearate	Magnesium stearate	Magnesium stearate
Colorant	Titanium dioxide	Opadry	Titanium dioxide	Titanium dioxide	Titanium dioxide		

MH, metformin hydrochloride; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.

tablets obtained from the Turkish and European markets were coded as TR and ER, respectively. The excipient contents of all MH tablets are presented in Table 1.

Dissolution Studies

Dissolution studies were performed on the seven IR MH tablets (1000 mg) commercially available in the Turkish (one reference and five generic tablets) and European (one reference tablet) drug markets. In accordance with the BCS-based biowaiver criteria, the dissolution studies were performed using a Sotax dissolution testing instrument (Binningerstrassefor, Basel, Switzerland) in USP Apparatus 2 (paddle method) at 50 rpm, using 900 mL of pH 1.2, 4.5, and 6.8 buffers as the dissolution medium. In accordance with the USP monograph, the dissolution test was performed in Apparatus 2 at 75 rpm, using 1000 mL of phosphate buffer (pH 6.8). Six replicates of all dissolution tests were conducted at 37 ± 0.5 °C. At predetermined time intervals (e.g., 5, 10, 15, 20, and 30 min), a 2-mL sample was withdrawn and then replaced with an equal volume of fresh medium. The withdrawn samples were passed through a 0.45-µm membrane filter, and a validated high-performance liquid chromatography (HPLC) method was used to detect the concentration of MH in the samples.

The dissolution profiles were compared by means of a similarity test. According to the US FDA, "the similarity factor (f_2) is the logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves" (*8*). If more than 85% of the drug is dissolved within 15 min, the dissolution profiles are considered similar without further mathematical calculation. On the other hand, if less than 85% is dissolved within 15 min, the f_2 value should be calculated. All dissolution profiles were compared by means of a model-independent approach (f_2-similarity factor) proposed by Moore and Flanner with the following equation (*24*):

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

where n is the number of time points, R_t is the dissolved amount of the reference formulation at time t, and T_t is the dissolved amount of the test formulation at time t. Dissolution profiles are considered similar when f_2 values are greater than 50.

Permeability Studies

Human colorectal adenocarcinoma cells that were obtained from the ATCC, USA (Caco-2, passage number 28–32) were seeded at 30,000 cells/well and grown as epithelial monolayers on polycarbonate membrane inserts of 24-well plates for use in determination of the apical to basolateral permeability of MH. Thincerts cell culture inserts (1.0 µm) were purchased from Greiner Bio-One, Germany. DMEM, supplemented with 10% FBS, penicillin (50 units/mL), and streptomycin (50 µg/mL), was used as the growth medium. At 21 days after

seeding, TEER values of the Caco-2 cells were determined by using a Millicell-ERS voltohmmeter (USA), and the cells with values of > 600 $\Omega.cm^2$ were utilized in the transport studies. HBSS (25 mM D-glucose and 10 mM HEPES) was used in all experiments as the transport medium. The solution of MH in transport medium was freshly prepared at a concentration of 80 µM. Commercially available tablets containing 1000 mg MH were powdered separately, and an appropriate amount of the homogeneous powder was dissolved in transport medium to obtain 80 µM MH. Drug-containing solutions were added to the apical side (250 µL), and drug-free transport medium was added to basolateral side (750 µL). Two hours after incubation (37 °C and 30 rpm), samples were taken from both the apical and basolateral sides, and then analyzed by using a validated HPLC method. Apical-to-basolateral permeability (P_{app}) values were calculated from the equation: P_{app} = rate of transport ÷ (surface area × initial concentration).

The results were compared by the Mann-Whitney U test using IBM SPSS Statistics 23. Differences between the results were considered significant for *p* values of < 0.05.

HPLC Analysis

The HPLC system used for analysis was Shimadzu LC-20 A/Prominence Alliance (Japan). MH was separated by using a Waters Spherisorb ODS2 C_{18} (250 × 4.6 mm, 5 µm; USA) column. The HPLC system was run at 25 °C with a mobile phase of phosphate buffer (pH 3; 100 mM) and acetonitrile (30:70 v/v), a 20-µL injection volume, and a flow rate of 1 mL/min. The diode array detector was fixed at 232 nm, and the retention time of MH was 2 min. Calibration curves were obtained for all media (pH 1.2, 4.5, and 6.8 buffers, and transport medium).

RESULTS AND DISCUSSION

Dissolution Studies

For an IR drug product of Class 3 compounds, the drug substance should exhibit high solubility (the highest single dose administered as IR formulation is completely dissolved in 250 mL buffer in the pH range of 1.2–6.8 at 37 ± 1 °C), with limited absorption (extent of absorption < 85%). In addition, very rapid (> 85% within 15 min) in vitro dissolution for the test and reference product within the range of pH 1–6.8 (pH 1.2, 4.5, and 6.8) should be shown. Moreover, excipients that may affect bioavailability should be qualitatively and quantitatively the same, and other excipients should be qualitatively the same and quantitatively very similar (*7, 8*). In dissolution studies, the FDA and EMA differ with respect to the volume of dissolution media (for USP Apparatus 2, FDA: 500 mL or less [or 900 mL if appropriately justified]; EMA: 900 mL or less in buffers of pH 1.2, 4.5, and 6.8) and rotation speed (for USP Apparatus 2, FDA: 50 rpm [or at 75 rpm when appropriately justified]; EMA: 50 rpm) (*7, 8*).

The dissolution results are presented in Table 2 and the dissolution profiles are displayed in Figure 1. For all MH tablets (reference and generic tablets), more than 75% of the labeled amount was dissolved at pH 6.8 phosphate buffer within 30 min, indicating that acceptance criteria stated in the USP monograph was fulfilled. In contrast, the in vitro dissolution criteria of the BCS-based biowaiver was fulfilled only by the generic tablet coded B (Tables 2 and 3). Neither the reference tablets (TR and ER) nor the other generic tablets (except tablet B) were very rapidly dissolved according to the BCS-based biowaiver criteria. Although all generic MH tablets were rapidly dissolved (more than 85% dissolved within 30 min in each buffers), the reference tablets (TR and ER) did not show rapid dissolution in all dissolution media (Table 3). The evaluation of dissolution profiles showed that the generic and reference tablets were not similar in the three dissolution media, although the reference tablets from Turkey and Europe were similar (Table 4).

Cheng et al. reported that two marketed IR 500 mg MH tablets were rapidly dissolved (both formulations released > 89% MH in 30 min) and showed similar dissolution profiles (USP Apparatus 1 at 100 rpm in 1000 mL of buffers at three different pH) and that the 90% confidence intervals for the ratio of means (AUC and C_{max}) were within the acceptance range of 80%–125% for the log-transformed data, indicating that the two IR products were bioequivalent in 12 healthy Chinese male volunteers (*9*). In our study, the dissolution profiles of generic tablets were not similar to reference tablets. As suggested by Cheng et al., in vivo absorption of MH is controlled by membrane permeability rather than dissolution and drug release (*9*). Therefore, MH bioavailability will be less dependent on its dissolution behavior. According to the EMA, "in the event that the results of comparative in vitro dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo the latter prevails" (*7*).

Permeability Studies

Caco-2 cells are used widely to determine the permeability of compounds (*25, 26*). Permeability studies across Caco-2 provide not only an initial assessment of the intestinal absorption, but also information on the possible effects of drug-excipient interactions on the absorption.

It was demonstrated that MH has concentration- and pH-dependent, non-saturable, non-polar and linear (for > 1 h) transfer across Caco-2 cells, with a P_{app} value of 5.5×10^{-6}

Table 2. Dissolution Results for Generic and Reference Tablets Containing 1000 mg MH (n = 6)

Tablets	BCS-Based Biowaiver (% dissolved)						USP-Monograph (% dissolved)	
	pH 1.2 buffer*		pH 4.5 buffer*		pH 6.8 buffer*		pH 6.8 phosphate buffer**	
	15 min	30 min	15 min	30 min	15 min	30 min	15 min	30 min
A	63.58 ± 5.37	100.5 ± 5.98	66.28 ± 6.42	92.62 ± 2.55	89.40 ± 7.59	100.95 ± 1.69	91.71 ± 1.12	96.66 ± 1.64
B	91.12 ± 4.14	105.12 ± 6.21	85.00 ± 4.30	95.82 ± 2.78	92.62 ± 4.11	100.38 ± 1.56	98.69 ± 1.08	97.06 ± 2.27
C	63.04 ± 9.14	91.16 ± 5.10	74.32 ± 7.39	96.74 ± 2.10	76.38 ± 3.75	98.50 ± 1.08	94.00 ± 2.82	98.04 ± 1.46
D	79.38 ± 2.88	96.91 ± 3.05	69.19 ± 5.75	94.46 ± 2.39	70.99 ± 7.57	95.92 ± 2.00	90.01 ± 1.92	96.81 ± 0.27
E	55.59 ± 4.76	88.73 ± 2.74	66.65 ± 5.54	96.06 ± 1.15	56.83 ± 5.69	89.15 ± 4.98	80.80 ± 9.73	98.49 ± 0.86
TR	31.10 ± 2.18	45.63 ± 3.06	38.41 ± 4.01	63.68 ± 4.80	37.95 ± 3.18	61.57 ± 4.64	59.10 ± 6.36	87.65 ± 7.26
ER	22.03 ± 2.58	30.46 ± 5.03	34.05 ± 2.13	50.5 0 ±3.17	45.09 ± 3.48	71.48 ± 5.58	64.36 ± 6.81	93.38 ± 7.00

*Values are expressed as mean ± SD. *Apparatus 2 (paddle), 50 rpm, 900 mL; ** Apparatus 2 (paddle), 75 rpm, 1000 mL. MH, metformin hydrochloride; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.*

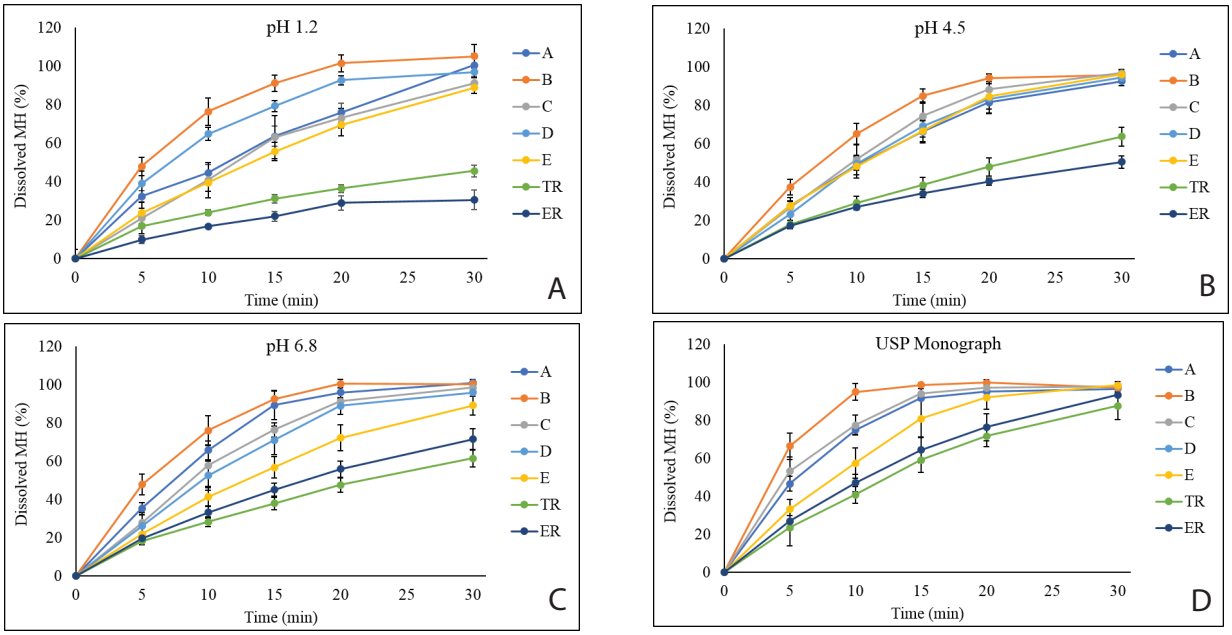

Figure 1. Dissolution profiles (mean ± SD; n = 6) of commercially available tablets containing 1000 mg MH in pH 1.2 (A), pH 4.5 (B), pH 6.8 (C) buffer mediums, and USP monograph conditions (D). MH, metformin hydrochloride; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.

Table 3. Dissolution Properties of Tablets Containing 1000 mg MH

Tablets	BCS-Based Biowaiver						USP-Monograph
	pH 1.2 buffer		pH 4.5 buffer		pH 6.8 buffer		pH 6.8 phosphate buffer
	Very Rapidly Dissolving*	Rapidly Dissolving**	Very Rapidly Dissolving	Rapidly Dissolving	Very Rapidly Dissolving	Rapidly Dissolving	Meets Criteria***
A	-	+	-	+	+	+	+
B	+	+	+	+	+	+	+
C	-	+	-	+	-	+	+
D	-	+	-	+	-	+	+
E	-	+	-	+	-	+	+
TR	-	-	-	-	-	-	+
ER	-	-	-	-	-	-	+

**More than 85% of the labeled amount of drug dissolves within 15 min; **More than 85% of the labeled amount of drug dissolves within 30 min; ***More than 75% of the labeled amount of drug dissolves within 30 min; + indicates that tablets meet the criteria specified in the column; - indicates that tablets do not meet the criteria specified in the column . MH, metformin hydrochloride; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.*

Table 4. Similarity (f_2) Values of Tablets Containing 1000 mg MH

		f_2 values			
Reference	**Generic**	**pH 1.2**	**pH 4.5**	**pH 6.8**	**USP**
TR	A	22.49	29.75	19.58	29.21
TR	B	12.99	21.31	16.99	21.02
TR	C	25.57	26.67	23.54	26.91
TR	D	17.15	28.56	25.84	30.56
TR	E	27.84	28.40	35.43	39.00
ER	A	17.34	24.79	23.48	33.54
ER	B	9.62	18.13	20.28	23.79
ER	C	19.88	22.29	28.43	30.75
ER	D	13.13	23.82	31.38	35.23
ER	E	21.54	23.65	44.97	46.47
ER	**TR**	**50.61**	**57.51**	**57.08**	**63.94**

MH, metformin hydrochloride; USP, United States Pharmacopeia; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.

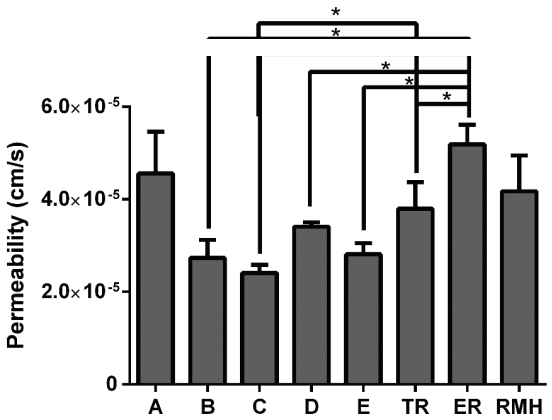

*Figure 2. Permeability values (mean ± SD; n = 3) of raw MH (RMH) and commercial tablets containing 1000 mg MH. *indicates statistical significance p<0.05. MH, metformin hydrochloride; TR, MH reference tablets from Turkish market; ER, MH reference tablets from European market; A, B, C, D, E: MH generic tablets obtained from Turkish market.*

cm/s at pH 7.4 (*27*). In another study, P_{app} and P_{app}, total (P_{app} + P_{app}, tissue, which is the value of time-dependent accumulation in the tissue) values of MH were reported as (6.67 ± 0.54) × 10^{-6} cm/s and (7.68 ± 1.62) × 10^{-6} cm/s, respectively, for human small intestinal and colonic mucosa by using the Ussing chamber technique (*28*). In addition, the permeability values of MH were reported by using the everted gut sac (7.37 × 10^{-7} cm/s) and Sartorius SM 16750 apparatus (6.13 × 10^{-7} cm/s) (*29*). In contrast, higher permeability values were determined for MH across the duodenum (4.5 × 10^{-5} cm/s), jejunum (3.3 × 10^{-5} cm/s), and ileum (3.0 × 10^{-5} cm/s) of rats (*30*). Our permeability value determined for raw MH (4.14 × 10^{-5} cm/s) was within the range of P_{app} values reported in the literature (Fig. 2). In vitro permeability across Caco-2 cells can be used to predict in vivo (small intestinal) absorption in humans. According to the Caco-2 permeabilities, the compounds are classified as poorly (0%–20%; P_{app} < 1 × 10^{-6} cm/s), moderately (20%–70%; P_{app} between (1–10) × 10^{-6} cm/s), and well (70%–100%; P_{app} > 10 × 10^{-6} cm/s) absorbed compounds (*31*).

There was no statistically significant difference between the MH permeability values determined for all reference and generic tablet formulations and the raw MH permeability value (p > 0.05), indicating that the excipients used in the tablets did not significantly change the MH permeability. However, a significant difference in permeability was observed for the two reference tablets. The tablet from Switzerland (ER) displayed higher MH permeability than the tablet from Turkey (TR) (p < 0.05) (Fig. 2). This may be related to the differences in the manufacturing processes, as both reference tablets contain the same excipients (Table 1).

Based on these results, the reference tablet chosen for the comparison of MH permeability between the reference and generic tablets is important. When the ER tablet was selected as the reference, the permeability of generic tablets B, C, D, and E was significantly lower (p < 0.05). However, when compared to the TR tablet, a significant decrease in MH permeability was observed for generic tablet C only (p < 0.05). Only generic tablet A had permeability similar to both reference tablets (Fig. 2). As shown in Table 1, tablets do not contain any excipients that might affect permeability, and no significant differences between raw MH and formulations were observed. In contrast, generic tablets B, D, and E displayed significantly lower MH permeability than the ER tablet. Although formulations of TR and ER tablets were qualitatively the same, and all generic formulations were similar to them, the difference may have been caused by active ingredient characteristics and production-related differences, given the high MH content.

HPLC Analysis

The results of HPLC analysis revealed that the method was simple and sufficiently sensitive to perform qualitative and quantitative analysis of MH from the dissolution and permeability samples and may be used for quality control studies of tablets containing 1000 mg MH. All calibration curves had determination coefficient (R^2) values > 0.999. Further, there was no interfering peak at the retention time of MH, indicating that the HPLC method used for analysis was selective.

CONCLUSIONS

MH, a BCS Class 3 drug with high solubility and low permeability, is a commonly used antidiabetic drug for the treatment of type II diabetes. We evaluated the dissolution and permeability properties of commercially available IR generic drugs obtained from the Turkish market and reference MH tablets obtained from Turkish and European markets. Except for generic tablet B, neither the generic nor the reference MH tablets fulfilled the very rapid dissolution criteria (> 85% in 15 min). The comparison of the dissolution profiles revealed that although the reference tablets obtained from Turkish and European (Swiss) markets were similar ($f_2 > 50$), none of the generic tablets were similar to either of the reference tablets. MH is a low permeability compound; therefore, the effect of excipients on the permeability of MH can alter bioavailability. Collectively, all results obtained from this study indicate that IR MH tablets do not meet the criteria for very rapid dissolution, as recommended by the guidelines for the BCS-based biowaiver for Class 3 compounds. Therefore, in vivo studies should be performed to demonstrate the bioequivalence of generic and reference tablet containing MH.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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