

Dissolution Profile Evaluation of Eight Brands of Metformin Hydrochloride Tablets Available in Jimma, Southwest Ethiopia

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Background: Dissolution is the critical quality control parameter and used to predict an in vivo oral bioavailability, and it is used to support bio-waiver.

Aim: To evaluate and compare the dissolution profile of eight brands of metformin HCL 500 mg tablets available in Jimma town, Southwest Ethiopia.

Methods: The study was conducted in Jimma town, Ethiopia. Eight (seven brands and one comparator) metformin HCL 500 mg tablets were included. The dissolution study was conducted as per United States Pharmacopeia, and the dissolution profile was compared by one-way ANOVA, model-dependent and model-independent approaches.

Results: All of the included tablet brands complied with single-point dissolution study specification. Statistical comparisons of the dissolution profile by one-way ANOVA revealed that all brands had similar dissolution profiles ($p=0.89$). All of the brands had a similarity factor (f_2) $>50\%$ and the difference factor (f_1) <15 . The entire brands followed the Weibull curve approach (the highest coefficient of determination and lowest Akaike Information Criteria) for the release of an active pharmaceutical ingredient.

Conclusion: All of the brands complied with single point dissolution study and all of them could be used interchangeably with the innovator drug. All brands followed the Weibull method for the release of the drug substance.

Keywords: dissolution, Jimma, metformin hydrochloride, biopharmaceutical classification

Introduction

According to a WHO 2016 report, diabetes mellitus is commonly classified as Type 1 or Type 2 diabetes. Type 2 diabetes was the major cause of total diabetes prevalence and affects every population. The number of patients with diabetes mellitus is increasing. Accordingly the number of adult patients was 422 million in 2014 worldwide. The prevalence was 4.7% in adults in 1980 which becomes 8.5% in the year 2014, and the rise was high in low- and middle-income countries.¹ Besides, according to an International Diabetes Federation projection there will be 552 million diabetic patients by 2030² and most of them will be living in low- and middle-income countries. Each year four million deaths in the world are attributed to diabetes mellitus, and in 2017 the annual expenditure was 850 billion US dollars. Unless otherwise halted the socioeconomic consequences will be huge.³⁻⁵ However, the World Health Organization reported that 30% of drugs sold in Africa were poor quality. This fact might be attributed to weak regulatory systems and/or limited resources.

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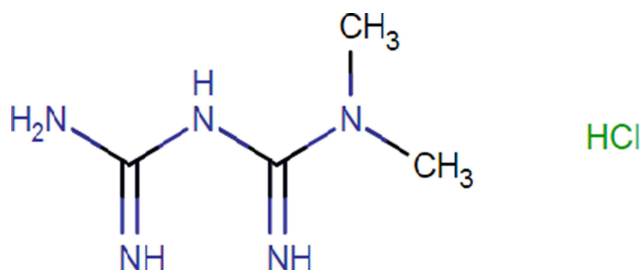


Figure 1 Chemical structure of metformin hydrochloride.

Chemically, metformin HCL was N, N-dimethyl-imido-dicarbonimidic diamide hydrochloride (Figure 1). The molecular weight of metformin is 129 Da and it has low solubility in lipid media. Due to this, the ability of the drug to pass the cell membrane is low.⁶

As per the Biopharmaceutics Classification System (BCS), it is class III drug.⁷ Therefore, permeability is the rate-limiting step in drug absorption. Dissolution is the critical quality control parameter for drugs as it has direct impact on absorption. Fast dissolution is required to enhance contact time of the dissolved drug with absorption mucosa. So, the duration of dissolution should be hardline for such drugs. In vitro in vivo correlation (IVIVC) serves as a surrogate for in vivo bioavailability and to support bio-waivers. IVIVCs could also be employed to establish dissolution specifications and to support and/or validate the use of dissolution methods.^{8,9} Dissolution as a quality control tool for forecasting in vivo performance of a drug product is significantly enhanced if an in vitro-in vivo relationship is established. The in vitro test serves as a tool to differentiate passable and impassable drug products. Passable products are bioequivalent in terms of in vivo performance and vice versa.¹⁰ The absorption of drugs after oral administration depends on various factors from which the release of the drug substance from the dosage form, its dissolution in physiological conditions, and its permeability through the gastrointestinal tract, and the tests are mainly used to assure the quality of the pharmaceutical product. Different methods for comparisons of dissolution profiles of different tablets are suggested by SUPAC-IR¹⁰ from those, statistical analyses by one-way analysis of variance, model-dependent and model-independent parameters are common.

Even though there are different brands of drugs introduced into the world pharmaceutical market to improve public health outcome, the proportion of poor quality drugs are increasing proportionally worldwide. The study done in Albania to check the interchangeability of three

brands of metformin HCL indicated that two of the brands could be used interchangeably.¹¹ Another study done in Asia (Qatar) to assess bioequivalence and interchangeability of 10 different brands of metformin hydrochloride revealed that only six of the brands could be used interchangeably with the comparator.¹² Similar to other parts of the world, the African continent as a whole is also facing a great challenge in the quality of medicines. The study done in Nigeria for comparative evaluation of the physicochemical properties of some commercially available brands of metformin HCL tablets on eight different brands showed that only four of the brands are bioequivalent and can be used interchangeably.¹³ Therefore, the aim of the study was to evaluate and compare dissolution profile of different brands of metformin hydrochloride tablets available in Jimma town.

Materials and Methods

Study Setting and Period

The study was conducted in Jimma town. The town is located 357 km southwest of Addis Ababa, the capital of Ethiopia. All private and public pharmacies available in the town were included in the study. The town is used as a commercial hub for the transaction of pharmaceuticals in the southwest region of the country. According to Ethiopian pharmaceutical supply agency of Jimma branch there are, eight wholesales, 33 drug vendors, four public drug shops in health centers, 23 private pharmacies, three public hospitals, and three private hospitals in the town. The laboratory work was done in Jimma University Laboratory of Drug Quality (JULaDQ). All brands included in the study were within their shelf life at the time of the study (Table 1). The work was conducted from July to August 2019.

Instruments

Analytical Balance (Mettler Toledo, Switzerland), RC-6D Dissolution Apparatus (Apparatus 2; Tian Jin Optical Instruments, China), UV-Vis Spectrophotometer (Cecil Instruments, UK), and Water Purification System (Thermo Scientific, Model-7143, USA) were used for the study.

Chemical and Reagents

Distilled water, sodium hydroxide (BDG Laboratory Supplies, Purity=97.5%), potassium dihydrogen orthophosphate (Techno Pharm Chem, Bahadurgarh, Purity=99–

Table 1 General Characteristics of Brands Included in the Study, 2019

Brands code	Man. Date	Exp. date
MT008*	10/2018	09/2023
MT004	07/2018	06/2023
MT001	12/2018	09/2021
MT007	08/2018	08/2022
MT005	06/2018	06/2021
MT006	07/2018	07/2021
MT002	06/2018	06/2023
MT003	12/2017	12/2020

Note: *Comparator.

101%, India) were used. The working standard of metformin hydrochloride was donated by the Ethiopian Food and Drug Administration Authority (EFDA).

Sampling Technique and Sample Collection

All available eight brands of metformin HCL 500 mg tablets were purchased from private and public drug retail outlets available in Jimma town by trained mystery shoppers. Since Ethiopia is one of the countries with weak medicine regulations, there might be outlets selling expired or unregistered medicines, which may make outlet staff suspicious and anxious about the investigations. Besides, in resource-poor countries, the medicine market is heavily segmented with different people of different spending power, and the mystery shopper approach was used to overcome this issue. The mystery shoppers were instructed simply to state that they are diabetic patients travelling somewhere and running out of their medication. The aim of the study was blinded for mystery shoppers and they were only instructed to collect the samples. The relevant information collected was the name of drug substance, country of origin, manufacturing company, expiry date, manufacturing date, and batch/lot number. Guidelines for field surveys of the quality of medicines proposed by Newton et al were used for sampling strategy.¹⁴ Only one brand was purchased from each outlet. The samples were kept in their original package, transported to Jimma University laboratory of drug quality (JuLaDQ), and stored under room temperature until the

analysis. General characteristics of brands included in the study are presented in Table 1.

Dissolution Test

Calibration Curve

A stock solution was prepared by dissolving 100 mg of metformin hydrochloride USP RS in 100 mL of phosphate buffer (pH 6.8). From the stock solution, six concentration levels (6, 7, 8, 9, 10, and 12 µg/mL) were prepared with phosphate buffer. Then, the absorbance was determined spectrophotometrically at a wavelength of 233 nm and plotted against the six concentration levels to draw the calibration curve.

Dissolution Profile

The test was conducted as outlined on the USP monograph on eight tablets of each brand using USP Apparatus II operated at 50 rpm. The dissolution medium was 1000 mL phosphate buffer (PH 6.8) maintained at 37°C±0.5°C. USP 2015 specifies that at a single time of 30 min, 80% of the drug substance needs to be dissolved.¹⁵ Samples of 10 mL was withdrawn at 5, 15, 30, and 45 minutes, and a fresh 10 mL dissolution medium was used to replace the withdrawn sample after each sampling, and then, the withdrawn samples filtered. After filtration and appropriate dilution (100×), the absorbance were measured by UV-visible spectrophotometer at a wavelength of 233 nm. Finally, the concentration was determined from the calibration curve of the standard solution having a known concentration of metformin hydrochloride RS in the same medium, and the percentage drug release was calculated each time. All of the experiments were done in triplicate.

Data Analysis

Microsoft Excel 2010 and SPSS version 20 software programs were used for statistical analysis. $p < 0.05$ were considered as statistically significant, and one-way ANOVA was carried out for comparison of the dissolution profile of metformin hydrochloride tablets. The dissolution profile of those tablets was also compared by the model-dependent and model-independent methods (Table 2).

Table 2: Model dependent and model independent parameters used to compare metformin hydrochloride tablet brands included in the study.

Table 2 Model dependent and model independent parameters used to compare metformin hydrochloride tablet brands included in the stud

Model Dependent	Model Independent
Zero order $Q = K.t + Q_0$	$f_1 = \left\{ \left[\frac{\sum_{i=1}^n [R_t - T_t]}{\sum_{i=1}^n R_t} \right] \right\} 100$ $f_2 = 50 \log \left\{ \left[+ \left(\frac{1}{n} \right) \sum_{i=1}^n (R_t - T_t)^2 \right]^{0.5} 100 \right\}$
First order $Q = Q_0 e^{k \cdot t}$	$DE = \frac{1}{Q_{100\text{st}}} \times 100$
Second order $\frac{1}{Q} = K.t + \frac{1}{Q_0}$	$MDT = \frac{\sum_{i=1}^n t_i^{AV} X \Delta Q_i}{\sum_{j=1}^n \Delta Q_j}$
Third order $\frac{1}{Q^2} = K.t + \frac{1}{Q_0^2}$	
Hixson–Crowell model $Q^{\frac{1}{3}} = K.(-T_{LAG}) + Q_0^{\frac{1}{3}}$	
Higuchi model $Q = K.\sqrt{t}$	
Weibull model $m = 1 - \exp \left[\frac{-(t/a)^b}{a} \right]$	
Best model criteria $R^2 = \frac{[N \cdot \sum_{i=1}^N (X_i \cdot Y_i) - \sum_{i=1}^N X_i \sum_{i=1}^N Y_i]^2}{[N \cdot \sum_{i=1}^N X_i^2 - (\sum_{i=1}^N X_i)^2] \cdot [N \cdot \sum_{i=1}^N Y_i^2 - (\sum_{i=1}^N Y_i)^2]}$ $AIC = 2K + N \cdot \left[\ln \left(\sum_{i=1}^N (Y_i - \bar{Y}_i)^2 \right) \right]$	
Where, Q_0 is the initial amount of drug substance Q is the amount of drug substance released at time, t t is time K is the rate constant T_{LAG} is lag time m is the amount of drug substance dissolved at time, t a is time constant b is shape parameter R^2 is coefficient of determination Y_i is observed value i is data point N is number of data points AIC is an Akaike information criterion K is rate constant, Y_i is observed values N is number of data points	Where, f_1 is difference factor f_2 is similarity factor n is the number of time points R_t is the dissolution value of the reference at time, t T_t is the dissolution value of the test drug at time, t DE is dissolution efficiency MDT is mean dissolution time $\Delta Q = Q_{(t)} - Q_{(t-1)}$, $t_i^{AV} = (t_i + t_{i-1})/2$, and n is amount of time points

Result

Calibration Curve

As shown on the calibration curve (Figure 2), a linear regression equation was $Y=0.0769X+0.0535$ with $r^2=0.9987$, where “Y” is the absorbance, and “X” is the concentration in $\mu\text{g/mL}$. By using this equation, the percentage drug substance released at times of 5, 15, 30, and 45 min were calculated.

Dissolution Study

At pharmacopeia time in 30 min, all of tablet released the recommended amount of drug substance as shown in Figure 3.

Mean Dissolution Time

The mean dissolution time for each brand included in the study is shown in Table 3. MT003 and MT006 had the highest and lowest mean dissolution time, respectively.

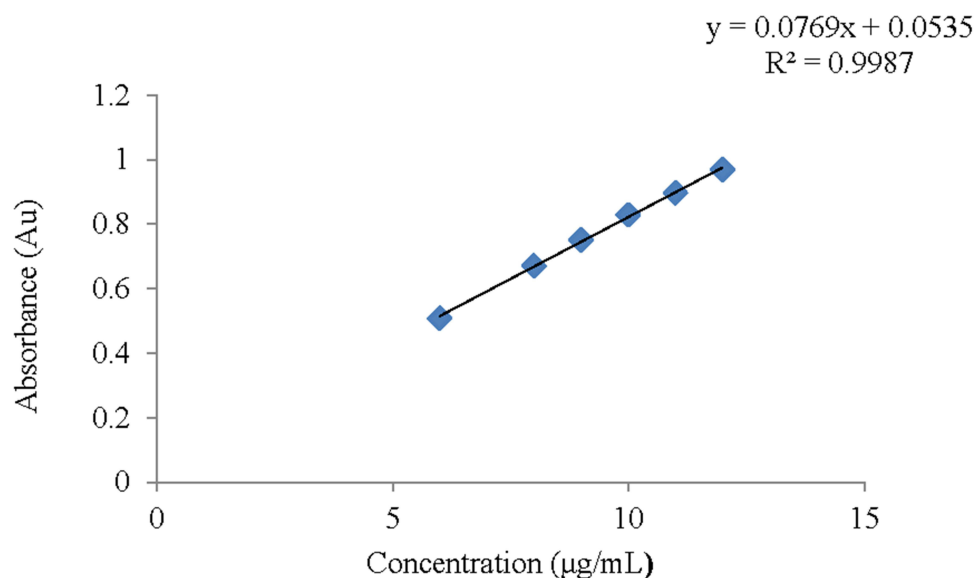


Figure 2 Calibration curve for dissolution study of metformin hydrochloride 500 mg tablets tested, 2019/2020.

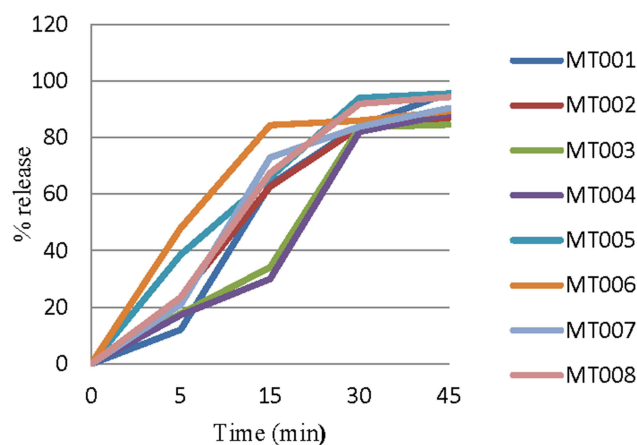


Figure 3 Dissolution profile (mean, n=6) of metformin hydrochloride 500 mg tablets included in the study, 2019.

Comparison of Dissolution Profile

Statistically, all of the tested drugs had a similar dissolution profile (Table 3). As per the fit factors, All brands had a similarity factor (f_2) of greater than 50% and difference factor (f_1) of <15. All of them had a difference in dissolution efficiency of within $\pm 10\%$ except MT003 and MT004 (Table 3).

Model-dependent Methods

The model-dependent approach showed that all of tested metformin HCL tablets were best explained by Weibull curve with highest determination coefficient (R^2) and lower AIC as shown in Table 4.

Discussion

Dissolution of a drug is an essential aspect for drug evaluation, and it is one of the most important control tests for assuring product uniformity and batch-to-batch equivalence. According to the present study, all the brands released the necessary amount of drug substance in 30 min as outlined on USP (>80% of drug substance needs to be dissolved).¹⁵ Even though statistical equivalence does not guarantee biopharmaceutical equivalence, all of the brands had a similar dissolution profile ($p > 0.05$). However, to study the dissolution profile of different brands 10 mL of samples were taken at 5, 15, 30, and 45 min (Figure 3) and there is a difference in dissolution profile of different brands. This difference might be attributed to difference in excipients used and difference in manufacturing process used by various manufacturing industries.

Mean dissolution time (MDT) characterizes the drug substance release from the dosage form and the retarding efficiency of the polymer. A higher value of mean dissolution time indicates the lowest rate of drug release from the dosage form. This in turn leads to the slow onset of action and higher drug-retaining ability of the polymer and vice versa.¹⁶ Accordingly, MT003 had the highest mean dissolution time. Therefore, the drug might be characterized by slow release of the drug from the dosage form and longer onset of action. However, MT006 had the minimum mean dissolution time, and so it may require a short time to dissolve, and might have a fast onset of action. This difference in mean dissolution time might be related to difference in manufacturing processes.

Table 3 Comparisons of Dissolution Profile of Metformin Hydrochloride 500 mg Tablets Included in the Study by Model Independent Parameters, Jimma Town, 2019 (n=3)

Brands code	Model Independent Approach		Dissolution Efficiency (%)	Difference of Dissolution Efficiency (Innovator-Tested Brands)	MDT	p-value
	f ₁	f ₂				
MT001	7.80	60.88	63.60	5.42	15.13	0.89
MT002	8.35	69.70	63.70	5.32	12.95	
MT003	8.32	69.26	54.59	14.53	18.82	
MT004	9.88	97.67	53.30	15.72	17.84	
MT005	2.08	4.33	72.01	-2.99	11.11	
MT006	6.14	37.67	74.99	-5.97	7.21	
MT007	8.06	65.00	66.79	2.23	11.75	
MT008 ^a	–	–	69.02	–	12.07	

Note: ^aComparator.

Abbreviations: MDT, mean dissolution time; f₁, difference factor; f₂, similarity factor.

Table 4 Comparisons of Dissolution Profile of Metformin HCL 500 mg Tablets Included in the Study by Model Dependent Approach; Jimma Town, 2019

Model dependent parameters	Tested tablet brands code								
	Parameters	MT001	MT002	MT003	MT004	MT005	MT006	MT007	MT008
zero	R ²	0.8398	0.8352	0.8819	0.9096	0.8663	0.6123	0.7275	0.8048
	AIC	29.9581	27.8774	28.1026	27.448	26.705	27.095	30.817	29.794
First	R ²	0.6822	0.7255	0.8711	0.8999	0.8166	0.5876	0.6351	0.7073
	AIC	35.2891	31.0839	32.2301	31.911	29.308	29.113	33.669	33.156
Second	R ²	0.5723	0.6321	0.8017	0.8453	0.7518	0.5671	0.5703	0.6194
	AIC	55.166	38.4199	43.4612	44.372	33.225	30.485	42.763	41.689
Third	R ²	0.5274	0.5710	0.7013	0.7508	0.6855	0.5508	0.5350	0.5622
	AIC	42.166	40.48558	40.5107	40.779	45.504	33.021	41.286	41.397
Hixson-Crowell	R ²	0.7334	0.7619	0.8803	0.9064	0.8354	0.5954	0.6635	0.7406
	AIC	32.9672	29.7878	30.5536	30.052	28.349	28.792	32.418	31.775
Higuchi	R ²	0.7154	0.9169	0.7583	0.7158	0.8941	-0.1546	0.8150	0.8809
	AIC	32.2569	25.1366	30.9685	32.030	25.774	32.688	29.267	27.818
Weibull	R ²	0.9759	0.9771	0.9308	0.9190	0.9718	0.8712	0.9334	0.9792
	AIC	23.8897	20.3587	26.0032	26.5406	19.388	23.259	25.601	18.618

Abbreviations: R², determination coefficient; AIC, Akaike Information Criteria.

To ascertain the interchangeability, the model-independent approach of similarity, and difference factor was used. To be interchangeable, the similarity factor should be 50–100, and the difference factor should be less than 15.¹⁰ Accordingly, all of the brands can be used interchangeably with the innovator as they have

a similarity factor of >50 and difference factor of <15. According to Anderson et al, for two drugs to be used interchangeably the difference of dissolution efficiency of innovator and tested drugs should be comparable with ±10% and vice versa.¹⁷ Thereupon, except MT003 all of the brands have difference in DE of within ±10%. This

report is different from a study in Saudi Arabia on six different brands of metformin hydrochloride and reported that five of the brands can be used interchangeably with the innovator drug.¹⁸ Another study conducted in Jordan revealed that from five brands of metformin hydrochloride, three of them were not bioequivalent with the innovator drug, and might not be used interchangeably in clinical practice.¹⁹ The study conducted on 10 brands of metformin HCL in Saudi Arabia in 2020 reported that nine of the brands were bioequivalent.²⁰ Whereas a study from Nigeria on eight brands of metformin HCL on the market reported that only four of them are interchangeable in clinical practice.¹³ This discrepancy might be due to the inclusion of different types of brands for the study. The model-dependent methods showed that all of the brands followed the Weibull curve method for the release of the drug substance.

Conclusion and Recommendations

As per the present study, all of the brands complied with single point USP pharmacopoeia specification for the release of the drug substance. Depending on fit factors and difference of dissolution efficiency criteria; all of the brands can be used interchangeably with the innovator drug. The model-dependent approach revealed that all of them followed the Weibull curve approach.

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Disclosure

The authors report no conflicts of interest in this work.

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