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Comparative Evaluation of Quality Attributes and In Vitro Dissolution Profile Similarity of Metformin Hydrochloride 500 mg Tablets Marketed in Sudan: Implications for Bioequivalence and Generic Interchangeability

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ABSTRACT

This study evaluated the physicochemical quality attributes and in vitro dissolution characteristics of five commercial brands of metformin hydrochloride 500 mg tablets (A–E) marketed in Khartoum, Sudan, to assess their quality and potential interchangeability with the innovator product (Brand A). Quality control tests were performed according to British Pharmacopoeia (BP) and United States Pharmacopeia (USP) specifications, including weight variation, hardness, friability, disintegration, assay by UV spectrophotometry, and dissolution profiling. Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, while dissolution profile similarity was assessed using the similarity factor (f_2). All brands complied with pharmacopeial requirements for weight uniformity, hardness, friability (0.0002–0.039%), and disintegration (<15 min). Brands A, C, D, and E met the acceptable assay range of 95.0–105.0% of the labeled claim, whereas Brand B failed (92.8%). Similarly, Brands A, C, D, and E satisfied the dissolution requirement ($Q \geq 80\%$ at 30 min), while Brand B released only $71.2 \pm 2.4\%$ ($p < 0.01$). Similarity analysis showed that Brands C ($f_2 = 83.1$) and E ($f_2 = 76.4$) were similar to the innovator, whereas Brands B ($f_2 = 41.6$) and D ($f_2 = 46.8$) were dissimilar. These findings highlight that single-point pharmacopeial compliance may not ensure biopharmaceutical interchangeability, emphasizing the value of multi-point dissolution profiling and f_2 analysis in regulatory oversight and post-marketing surveillance.

Keywords: Metformin hydrochloride; Quality control; Generic interchangeability; *In vitro* dissolution profiling; Similarity factor (f_2); Post-marketing surveillance.

1. INTRODUCTION

Diabetes mellitus (DM) remains a critical global public health concern, with Type 2 diabetes mellitus (T2DM) accounting for 90% to 95% of all clinical cases^{1,2}. The epidemiological burden of T2DM has shifted rapidly toward developing countries, placing substantial socioeconomic and clinical strains on healthcare systems^{3,4}. In Sudan, this metabolic challenge is highly pronounced, with the International Diabetes Federation (IDF) reporting a national adult prevalence of approximately 19%, affecting nearly 3.86 million individuals⁵. Regional population-based surveys consistently demonstrate high prevalence trajectories across northern, eastern, and central states, driven by rapid urbanization and changing dietary habits⁶⁻⁹. To manage this extensive clinical burden, metformin hydrochloride, a biguanide oral antihyperglycemic agent that reduces hepatic gluconeogenesis and improves peripheral insulin sensitivity, is universally utilized as the first-line pharmacotherapy¹⁰⁻¹².

Maintaining the therapeutic efficacy and safety of essential medicines such as metformin requires rigorous pharmaceutical quality control and ongoing post-marketing surveillance¹³. Pharmaceutical analysis plays a central role in quality assurance by enabling the accurate identification, quantification, and physicochemical characterization of active pharmaceutical ingredients (APIs) in finished dosage forms¹⁴. In developing markets, the increasing availability of multisource generic medicines has substantially improved access and affordability for economically vulnerable populations. However, this expansion also raises concerns regarding the entry of substandard, falsified, or counterfeit products into the pharmaceutical supply chain¹⁵. Both innovator and generic products remain vulnerable to sophisticated counterfeiting practices, which may involve incorrect APIs, sub-therapeutic dosing, or fraudulent packaging^{16,17}. When evaluated using compendial quality control tests, such substandard formulations fail to comply with official pharmacopeial specifications, thereby compromising therapeutic outcomes and patient safety¹⁸. Even among legitimate manufacturers, variability among generic products can present distinct biopharmaceutical challenges¹⁹.

Minor variations in manufacturing techniques, excipient composition, compression parameters, and storage conditions can significantly influence the mechanical strength, disintegration behavior, and dissolution profiles of solid oral dosage forms^{20,21}. Major agencies have reinforced the adoption of a Quality by Design (QbD) approach, encouraging the implementation of systematic, science-based strategies in drug product development. Beyond formulation design, QbD principles

are also widely applicable across API synthesis, analytical and dissolution method development, manufacturing processes, and stability testing²². Consequently, continuous comparative quality evaluations of marketed drug products are vital for confirming their compliance with recognized pharmacopeial benchmarks and ensuring therapeutic potential for clinical interchangeability²³.

Although multi-brand quality assessments conducted in various regional markets have consistently demonstrated that metformin hydrochloride tablets generally comply with rigorous compendial standards for weight uniformity, hardness, friability, disintegration, and assay, these findings cannot be universally extrapolated to all markets²⁴⁻²⁹.

In Sudan, the complex interplay of socioeconomic pressures, evolving regulatory frameworks, and challenging climatic conditions creates a distinct risk profile for pharmaceutical products throughout the supply chain. Consequently, localized post-marketing surveillance is essential to ensure that medicines maintain their quality, safety, and efficacy under real-world storage and use conditions. In response to this need, the present study aimed to evaluate and compare the physicochemical quality attributes and *in vitro* dissolution profiles of commercially available 500 mg metformin hydrochloride tablet brands marketed in Sudan. The study further assessed dissolution profile similarity relative to the innovator product to provide evidence regarding the potential biopharmaceutical equivalence and interchangeability of these products, thereby supporting evidence-based regulatory decision-making and strengthening post-marketing quality surveillance in the Sudanese pharmaceutical market.

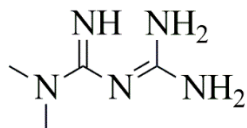
2. MATERIALS and METHODS

2.1 Materials

Five commercial brands of metformin hydrochloride 500 mg tablets (Figure 1) were obtained from community retail pharmacies in Khartoum, Sudan, and assigned codes **A–E** to preserve manufacturer anonymity. Among these, two brands were locally manufactured in Sudan (Brands **D** and **E**), while three were imported: Brand **A** (France, as innovator), Brand **B** (India), and Brand **C** (Saudi Arabia).

Deionized water and analytical-grade reagents, including hydrochloric acid (Fluka, Austria), potassium dihydrogen phosphate (Sigma, USA), and sodium hydroxide pellets (Merck, South Africa), were supplied by the Department of Pharmaceutics, College of Pharmacy, Sudan University of Science and Technology. The metformin hydrochloride reference standard (*RS*) was

generously provided by Amipharma Laboratories Ltd. (Khartoum, Sudan) and was used without further purification. All reagents were used as received without further purification.



IUPAC Name: 3-(diaminomethylidene)-1,1-dimethylguanidine

Chemical Formula: C₄H₁₁N₅

Exact Mass: 129

Figure 1: The chemical structure, IUPAC name, and molecular weight of Metformin

2.2 Study Design and Sampling

This was a comparative cross-sectional experimental study conducted to evaluate the physicochemical quality of five brands of metformin hydrochloride 500 mg tablets commercially available in community pharmacies in Khartoum, Sudan. The study was carried out in the Department of Pharmaceutics, College of Pharmacy, Sudan University of Science and Technology, over three months, from January to March 2026.

A purposive sampling technique was employed to select the five most frequently dispensed brands of metformin tablets, designated as Brands A–E, to ensure anonymity. Selection was based on market availability and dispensing frequency, as verified through consultation with community pharmacists and pharmacy stock records. Samples were purchased from five independent community pharmacies distributed across three major localities in Khartoum State (Khartoum, Omdurman, and Bahri) to enhance geographic coverage and minimize location-based bias.

From each brand, tablets were obtained from a single batch per product available at the time of purchase. Only products registered with the National Medicines and Poisons Board (**NMPB**) were included. Inclusion criteria required that products had at least six months of remaining shelf life at the time of purchase, were supplied in intact and sealed original packaging, and were commonly dispensed across at least three of the selected pharmacies. All samples were transported and stored under manufacturer-recommended conditions until analysis to preserve product integrity. Exclusion criteria included metformin tablets of other strengths (850 mg and 1000 mg), expired or near-expiry products, unregistered or suspected counterfeit products lacking **NMPB** approval, duplicate products from the same manufacturer (either generic or branded variants of the same formulation), and tablets obtained from packaging showing evidence of tampering, physical damage, or improper storage conditions, including exposure to excessive heat or moisture.

Regarding sample size determination, the number of tablets required for analysis was guided by the minimum requirements specified in the United States Pharmacopeia (USP) and British Pharmacopoeia (BP) for the relevant quality control tests. The uniformity of weight test requires a minimum of 20 tablets per brand, which represents the largest sample size required among all conducted tests. Because the same tablets were used sequentially for multiple evaluations, including weight variation, hardness, friability, disintegration, and dissolution testing, a minimum of 20 tablets per brand was considered sufficient to complete all required analyses. Accordingly, five samples of 20 tablets per brand were analyzed, giving a total of 100 tablets per brand.

To account for potential losses due to handling damage or retention samples, an additional 10–15% of tablets (approximately 10–15 tablets per brand) were procured, resulting in a total purchase of approximately 115 tablets. All experiments were conducted in triplicate (345 tablets/brand) to ensure analytical reliability and reproducibility, and results were expressed as mean $\pm$ standard deviation (SD).

Data were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc multiple comparison test to identify differences in mean values among the five brands. A *p*-value of < 0.05 was considered statistically significant. As the study involved commercially available pharmaceutical products, no human or animal subjects were involved, and it was classified as an *in vitro* laboratory-based quality control study.

2.3 Experimental Procedures

All procedures were carried out in accordance with the standards of the British Pharmacopoeia³⁰, the United States Pharmacopoeia³¹, and an established method adapted from the literature. Where applicable, tests were performed using independent tablet units, and results were expressed as mean $\pm$ standard deviation to ensure statistical reliability.

2.3.1 Visual and Physical Evaluation

The physical characteristics of the different metformin hydrochloride tablet brands, including shape, size, and color, were assessed by visual inspection. In addition, the thickness and diameter of five randomly selected tablets per brand were measured using a calibrated vernier caliper. The obtained data were used to calculate the mean values and SD for each brand³¹.

2.3.2 Friability Test

Friability testing was conducted to evaluate the mechanical strength and resistance of tablets to abrasion, in accordance with BP specifications. For each brand, ten tablets were randomly selected, de-dusted, and accurately weighed to determine their initial mass (W_0).

The tablets were then placed into the drum of a friability tester (EF-2L, Electrolab, India) at 25 rpm for 4 minutes (100 revolutions). After completion of the rotation cycle, tablets were removed, dedusted again, and reweighed to obtain the final mass (W_f). The percentage friability was calculated using Equation 1:

$$\text{Friability (\%)} = ((W_0 - W_f) / W_0) \times 100 \text{ ————— Equation 1}$$

Where W_0 is the initial mass of the tablets, and W_f is the final mass after the test ³¹.

2.3.3 Hardness Test

Tablet hardness was evaluated to determine resistance to mechanical stress and potential handling damage. For each brand, ten randomly selected tablets were tested using a Monsanto-type hardness tester. Each tablet was placed between the jaws of the instrument, and increasing radial force was applied until the tablet fractured. The breaking force required to cause tablet failure was recorded for each unit, and the mean hardness $\pm$ standard deviation was calculated for each brand. The obtained values were compared with pharmacopeial quality control expectations to assess mechanical integrity and batch consistency in accordance with USP guidelines ³¹.

Tablet breaking force was evaluated as a non-compendial quality attribute in accordance with the USP General Information Chapter. Because specific numerical hardness ranges are not mandated within individual compendial monographs, an empirical industrial baseline of ≥ 40 N (Newtons) was applied to verify mechanical resistance ³², supported by official USP compliance criteria for tablet friability and disintegration.

2.3.4 Uniformity of Weight Test

The uniformity of dosage units was evaluated using the weight variation test in accordance with United States Pharmacopeia (USP) guidelines ³¹. Twenty tablets were randomly selected from each commercial brand and individually weighed using an analytical balance (ELB 3000, Shimadzu, Japan). The mean weight for each sample was calculated, and the percentage deviation of each tablet from the mean was determined. According to USP specifications for tablets weighing more than 324 mg, a batch complies with the requirement if not more than two individual tablets deviate from the mean by more than $\pm 5\%$, and no single tablet deviates by more than $\pm 10\%$.

2.3.5 Disintegration Test

The disintegration test was performed in accordance with compendial specifications using a standard disintegration apparatus (Electrolab, India). For each commercial brand, six tablets were individually placed in the basket-rack assembly. The assembly was immersed in 900 mL of distilled water, maintained at $37 \pm 0.5^{\circ}\text{C}$ throughout the test. The apparatus was operated continuously, and the time required for each tablet to completely disintegrate and pass through the mesh screen was recorded. The disintegration time for each batch was expressed as mean $\pm$ standard deviation (SD) ²⁵.

2.3.6 Assay Test

The quantitative determination of the active API was performed to verify compliance with the labeled claim of metformin hydrochloride. Twenty tablets from each commercial brand were individually weighed and finely powdered using a mortar and pestle. A portion of the powder, accurately weighed to contain 0.1 g of metformin hydrochloride, was transferred into a volumetric flask, vigorously shaken with 70 mL of distilled water, and diluted to a final volume of 100 mL. The resulting suspension was filtered, and the first 20 mL of the filtrate was discarded to saturate the filter paper and prevent adsorption loss. A 10 mL aliquot of the clear filtrate was diluted to 100 mL with distilled water, and 10 mL of this solution was further diluted to 100 mL to obtain the final target working concentration. The absorbance of the final solution was measured at the maximum absorption wavelength (λ_{max}) of 232 nm using a UV-visible spectrophotometer. The percentage content of metformin hydrochloride was calculated utilizing the specific absorbance value $A^{(1\%, 1\text{cm})}$ of 798 at 232 nm. The UV spectrophotometric method used for quantification was based on BP ³⁰ and verified in-house for system suitability before analysis in accordance with the International Council for Harmonization (ICH) Q2(R2) guidelines³³.

2.3.7 In Vitro Dissolution and Analytical Method Verification

The *in vitro* dissolution profiles of the metformin hydrochloride tablets were evaluated using an established method adapted from the literature ²⁴. Testing was conducted using a USP Apparatus II (paddle method) dissolution tester (Labindia Analytical, India) operated at a rotation speed of 50 rpm. For each batch, six tablets were evaluated individually in 900 mL of pH 6.8 phosphate buffer solution, which was maintained at a controlled temperature of $37 \pm 0.5^{\circ}\text{C}$ throughout the procedure.

At designated time intervals (10, 20, 30, 45, 60, 75, and 90 min), a 5 mL aliquot of the dissolution medium was withdrawn from each vessel and immediately replenished with an equivalent volume

of fresh, pre-warmed medium to maintain constant sinking volume conditions. The withdrawn samples were filtered, appropriately diluted, and analyzed using a UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) at the maximum absorption wavelength (λ_{max}) of 233 nm against a phosphate buffer blank.

The UV spectrophotometric method used for quantification was based on previously validated literature protocols²⁴ and verified in-house for system suitability before analysis in accordance with the International Council for Harmonization (ICH) Q2(R2) guidelines³³, confirming acceptable linearity, accuracy, precision, and sensitivity. Quantitative determination of cumulative drug release was achieved using a standard six-point calibration curve, 2 to 8 $\mu\text{g/ml}$, constructed using a metformin HCl reference stock solution systematically diluted in the same buffer medium. To quantitatively evaluate and compare the *in vitro* dissolution profiles of the test formulations against the reference standard, the similarity factor (f_2) was determined. The f_2 factor is a logarithmic, reciprocal-square-root transformation of the sum of squared errors, serving as a reliable metric for the closeness of two release curves. The calculation was performed using Equation 2:

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

Where n is the total number of sampling time points, R_t is the cumulative dissolution percentage of the reference standard at time t , and T_t is the cumulative dissolution percentage of the test formulation at the corresponding time interval. Generally, f_2 values ranging between 50 and 100 indicate equivalence or high similarity between the two dissolution profiles²⁴.

3. RESULTS

3.1 Visual and Physical Evaluation Results

The visual and physical characteristics of five commercially available brands of metformin hydrochloride tablets (500 mg) were evaluated to assess compliance with pharmacopoeial quality standards. A summary of tablet shape, color, diameter, and thickness, along with the relevant acceptance criteria, is presented in Table 1. Diameter and thickness values are expressed as mean $\pm$ standard deviation.

All tested brands complied with the established visual and physical specifications. Organoleptic examination showed that all tablets exhibited smooth, uniform surfaces and were free from

observable defects such as capping, chipping, or mottling. Based on tablet geometry, the products were classified into two morphological groups: elongated caplet-shaped tablets (Brands **A** and **C**) and standard round tablets (Brands **B**, **D**, and **E**), with high consistency observed within each brand. Quantitatively, variations in thickness and diameter remained within the $\pm 5\%$ deviation limits specified by the United States Pharmacopoeia ³¹. The low standard deviation values ($SD \leq 0.06$ mm) indicate minimal variability within each brand, suggesting consistent manufacturing processes and uniform tablet compression across the evaluated products.

Table 1: Visual and Physical Characteristics of Metformin Hydrochloride Tablets (Brands **A–E**) (n= 3).

Brand Code	Visual Shape	Color	Average Diameter $\pm$ SD (mm)	Average Thickness $\pm$ SD (mm)	Acceptance Status
Brand A	Caplet (Elongated)	White	16.12 ± 0.04	5.12 ± 0.05	Passed
Brand B	Round, Biconvex	Off-White	12.15 ± 0.02	4.88 ± 0.03	Passed
Brand C	Caplet (Elongated)	White	15.98 ± 0.05	5.45 ± 0.04	Passed
Brand D	Round, Flat- faced	White	11.85 ± 0.03	5.02 ± 0.06	Passed
Brand E	Round, Biconvex	White	12.40 ± 0.03	5.31 ± 0.02	Passed
Acceptance Limits	Uniform within batch	Uniform within batch	$\pm 5\%$ of the mean batch diameter	$\pm 5\%$ of the mean batch thickness	USP/BP Compliance

3.2 Evaluation of Mechanical Strength, Disintegration, and Weight Uniformity

To comprehensively assess the post-compression quality and structural integrity of the five commercial metformin hydrochloride brands (**A–E**), evaluations of friability, crushing strength (hardness), and disintegration time were conducted. The results are presented in Table 2.

Additionally, the uniformity of dosage units across the five brands of metformin hydrochloride (500 mg) was assessed using the weight variation test. The calculated composite and individual weights, standard deviations, directional percentage deviations, and corresponding compliance outcomes are detailed in Table 3.

Table 2: Hardness, Friability, and Disintegration Time of Commercial Metformin Hydrochloride Tablets (Brands A–E) with Reference Acceptance Limits (n= 3).

Brand Code	Hardness $\pm$ SD (N)	Friability (%)	Disintegration Time $\pm$ SD (min)	Final Acceptance Status
A	85.4 $\pm$ 6.1	0.006	6.5 $\pm$ 0.8	Passed
B	79.2 $\pm$ 5.3	0.036	8.2 $\pm$ 1.1	Passed
C	91.6 $\pm$ 4.8	0.009	5.9 $\pm$ 0.6	Passed
D	52.1 $\pm$ 3.9	0.0002	4.1 $\pm$ 0.5	Passed
E	68.5 $\pm$ 5.7	0.039	7.3 $\pm$ 0.9	Passed
Acceptance Limits	$\geq$ 40 N	< 1%	$\leq$ 15 minutes for uncoated	Pharmacopoeial Criteria

Table 3: Weight Uniformity Analysis of Commercial Metformin Hydrochloride Tablets (Brands A–E) (n= 3).

Brand Code	Weight of 20 tablets (mg)	Average weight per tablet $\pm$ SD (mg)	Maximum weight of tablet (mg)	Minimum weight of tablet (mg)	Positive Deviation (%)	Negative Deviation (%)	Total number of tablets outside the USP specification	Status
A	10850.0	542.5 $\pm$ 4.2	549.3	534.1	1.25%	-1.55%	0	Passed
B	11162.0	558.1 $\pm$ 8.9	571.4	540.2	2.38%	-3.21%	0	Passed
C	10788.0	539.4 $\pm$ 5.1	547.8	530.2	1.56%	-1.71%	0	Passed
D	11020.0	551.0 $\pm$ 7.3	563.8	537.6	2.32%	-2.43%	0	Passed
E	10924.0	546.2 $\pm$ 6.0	556.0	535.4	1.79%	-1.98%	0	Passed

Adherence to the official specifications of the United States Pharmacopeia (USP) served as the benchmark for determining the quality and batch homogeneity of the procured retail formulations.

3.3 Quantitative Content Determination (Assay Test)

The quantitative determination of the API was performed to verify compliance with the labeled claim of metformin hydrochloride (500 mg). The percentage content of metformin hydrochloride was calculated from the ultraviolet (UV) absorbance values at $\lambda_{\text{max}} = 232\text{nm}$, using the standard specific absorbance $A^{(1\%, 1\text{cm})}$ of 798 at 232 nm. The consolidated assay results and their official pharmacopoeial compliance status are presented in Table 4.

Table 4: Chemical Assay and Content Uniformity Profiles of Metformin Hydrochloride Tablets (Brands A–E) (n = 3).

Brand Code	Absorbance at 232 nm	Mean API Content (mg)	Percentage Labeled Claim (%) $\pm$ SD	Acceptance Status
A	0.802	502.5	100.5% $\pm$ 1.1	Passed
B	0.741	464.3	92.8 % $\pm$ 1.4	Not Passed
C	0.789	494.4	98.87 % $\pm$ 0.9	Passed
D	0.765	479.3	95.6 $\pm$ 1.8	Passed
E	0.811	508.1	101.63 % $\pm$ 1.5	Passed
Acceptance Limits			95.0% – 105.0%	BP Pharmacopoeial Criteria

3.4 *In Vitro* Dissolution Analysis

The *in vitro* release kinetics of the API from five commercial metformin hydrochloride tablet brands (Brands A–E) were evaluated using USP Apparatus II in phosphate buffer medium (pH 6.8). To facilitate accurate quantification of the dissolved drug, a standard calibration curve was established using a series of systematic dilutions of a metformin hydrochloride reference stock solution within the same buffer. The resulting working standards encompassed a concentration range of 2 to 8 $\mu\text{g/mL}$ and were analyzed spectrophotometrically at the maximum absorption wavelength (λ_{max}) of 233 nm. The standard curves demonstrated excellent linearity, consistently yielding a coefficient of determination ($R^2 > 0.99$). The derived linear regression equations used to calculate the cumulative drug release percentages are illustrated in Figure 2. Quantitative cumulative drug release percentages across seven designated sampling intervals spanning 90 minutes are compiled in Table 5 and Figure 3. Brand A was selected as the innovator for the subsequent mathematical calculation of profile similarity factors (f_2). Dissolution data are expressed as mean percentage $\pm$ standard deviation (n = 6 vessels per product Brand). To comply with official pharmacopoeial quality baselines, the product must meet the standard acceptance threshold (Q), defined as the minimum percentage of labeled API required to dissolve within a specified time frame³⁴. For this study, the baseline mandate dictates that a minimum of 80% (Q) of the API must successfully dissolve within 30 minutes, satisfying the established pharmacopoeial immediate-release criteria, before evaluating further stage tolerances³⁵.

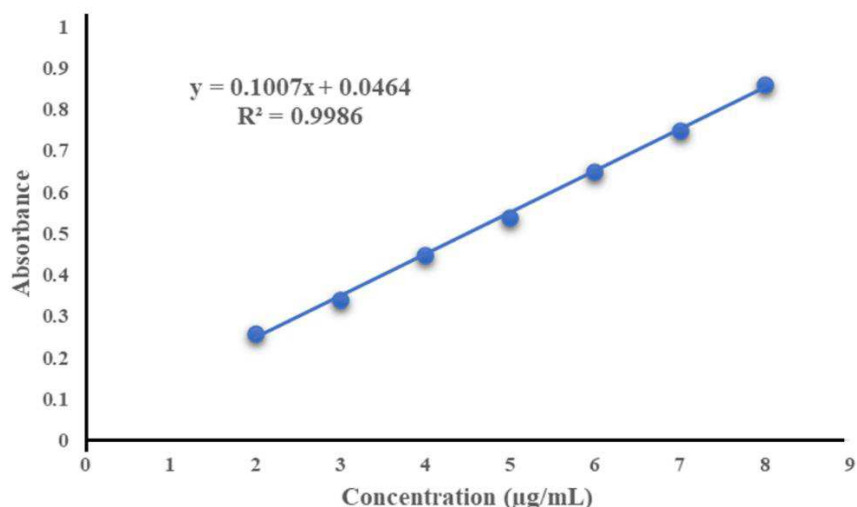


Figure 2. Metformin hydrochloride reference standard calibration curve.

Table 5: Cumulative In Vitro Dissolution Profiles and Similarity Factor (f_2) Values of Metformin Hydrochloride Formulations

Sampling Time (min)	Cumulative <i>In Vitro</i> Dissolution Profiles (mean, $\pm$ SD)				
	Brand A (%)	Brand B (%)	Brand C (%)	Brand D (%)	Brand E (%)
	(innovator)				
10	38.4 $\pm$ 2.1	26.1 $\pm$ 3.2	40.2 $\pm$ 1.9	51.6 $\pm$ 4.1	35.4 $\pm$ 2.8
20	62.1 $\pm$ 1.8	49.5 $\pm$ 2.9	65.4 $\pm$ 2.2	78.3 $\pm$ 3.5	59.8 $\pm$ 2.1
30	84.6 $\pm$ 1.5	71.2 $\pm$ 2.4	86.1 $\pm$ 1.7	94.2 $\pm$ 2.2	82.1 $\pm$ 1.9
45	96.2 $\pm$ 1.1	82.4 $\pm$ 1.9	97.8 $\pm$ 1.2	99.4 $\pm$ 0.8	95.3 $\pm$ 1.3
60	99.4 $\pm$ 0.6	89.6 $\pm$ 1.5	99.8 $\pm$ 0.4	99.7 $\pm$ 0.5	99.1 $\pm$ 0.7
75	99.8 $\pm$ 0.3	93.1 $\pm$ 1.1	100.1 $\pm$ 0.2	99.9 $\pm$ 0.2	99.6 $\pm$ 0.4
90	100.0 $\pm$ 0.1	95.4 $\pm$ 0.8	100.2 $\pm$ 0.1	100.0 $\pm$ 0.1	99.8 $\pm$ 0.2
(f_2)	Reference	41.6	83.1	46.8	76.4
Profile Status	Innovator	Dissimilar	Similar	Dissimilar	Similar

Based on the data provided in Table 5 and the pharmacopoeial baseline requirement of $Q = 80\%$ at 30 minutes, the evaluated brands exhibit distinct compliance profiles. Brand A (innovator) safely satisfies the baseline requirement with a mean dissolution of 84.6 %. Similarly, Brand C (86.1%), Brand D (94.2 %), and Brand E (82.1 %) all successfully meet the $Q \geq 80\%$ threshold at the 30-minute interval. In contrast, Brand B fails to meet the standard pharmacopoeial baseline, achieving a mean release of only 71.2 %. This delayed release kinetics directly supports its designation as "Dissimilar" ($f_2 = 41.6$) relative to the innovator standard. Conversely, although Brand D

comfortably exceeds the minimum Q baseline as the fastest-dissolving product, its rapid dissolution profile deviates so substantially above the reference curve that it is also categorized as mathematically dissimilar ($f_2 = 46.8$).

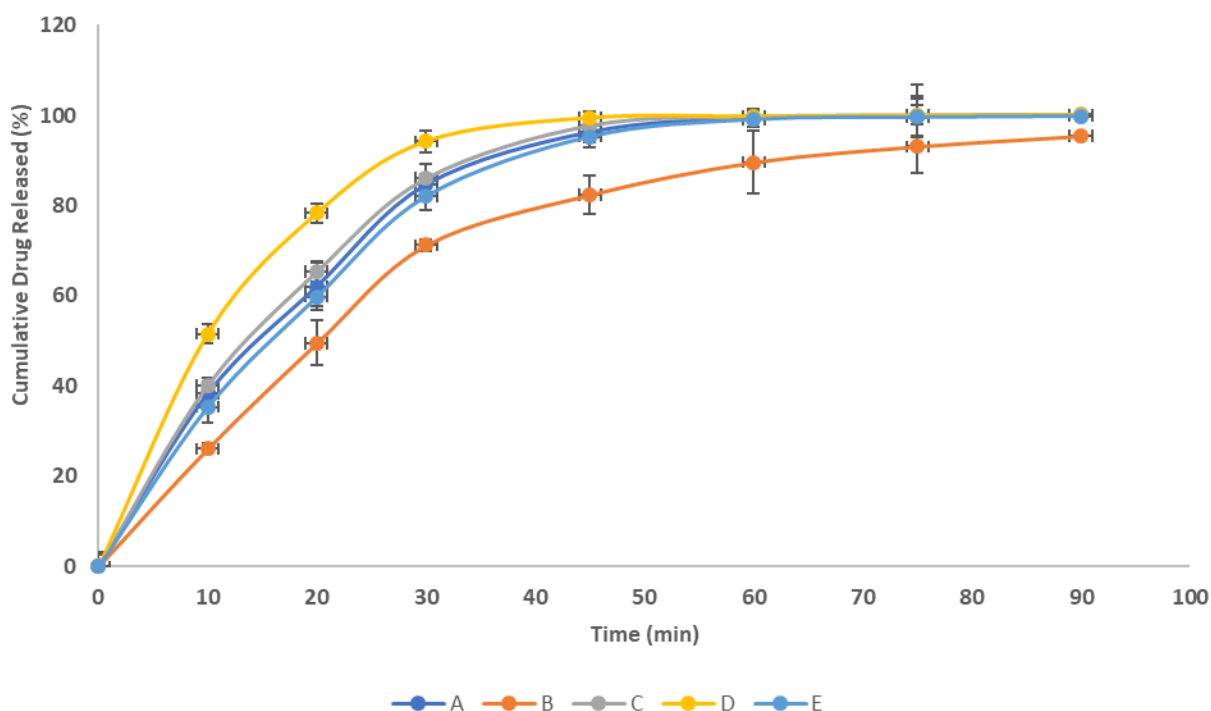


Figure 3. Comparative *in vitro* dissolution profiles of various metformin hydrochloride tablet brands (A to E). Each data point is expressed as the mean of six replicate measurements (n=6).

4. DISCUSSION

The present study demonstrates that while all evaluated metformin hydrochloride 500 mg brands complied with standard pharmacopoeial benchmarks for physical integrity and mechanical strength, notable discrepancies were evident in active chemical content, dissolution kinetics, and overall profile similarity. These findings align with a well-recognized limitation in generic drug surveillance: basic compliance with individual compendial tests does not inherently guarantee comprehensive pharmaceutical equivalence or biopharmaceutical interchangeability³⁶.

The biopharmaceutical transition of API from a solid compressed state to an absorbable solution is fundamentally governed by its disintegration rates and subsequent dissolution kinetics. Chemically, immediate-release metformin hydrochloride functions as a highly water-soluble, Biopharmaceutics Classification System (BCS) Class III molecule characterized by high solubility and low intestinal permeability^{37,38}. Because of its high individual dosage requirements (500 mg),

it demands a comparatively large structural tablet mass. Although its rapid intrinsic solubility generally aids dissolution in standard gastric environments, variations in core structural matrix compression forces, high solid-to-solvent mass ratios, and the specific choice of hydrophobic binders or commercial excipients can fundamentally alter disintegration behavior and delay immediate disintegrant fracturing^{36,39}.

The reduced assay value and suboptimal dissolution performance observed in Brand **B** suggest underlying deficiencies in formulation quality and manufacturing consistency. Although macroscopic evaluation indicated acceptable physical properties, the lower active content implies possible non-uniform drug distribution, inadequate blending, or suboptimal process control during granulation and compression. Such inconsistencies at the formulation level can reduce effective drug availability at the tablet matrix interface, thereby impairing dissolution performance despite acceptable tablet appearance and mechanical characteristics. This dissociation between physical quality and chemical performance highlights the importance of incorporating assay and dissolution testing as mandatory components of post-marketing surveillance.

In contrast, Brand **D** showed faster disintegration and a higher dissolution rate than the reference product. This behavior is likely attributable to formulation-driven factors such as reduced tablet hardness, increased porosity, or a higher proportion of superdisintegrants, which facilitate rapid medium penetration and tablet breakup. However, the same attributes that enhance dissolution rate may also alter release kinetics relative to the innovator product, as reflected in its lower similarity factor (f_2) despite high overall drug release. This finding underscores that accelerated drug release is not inherently indicative of improved equivalence and may instead reflect deviation from the reference release profile^{38,40}.

Integrated evaluation using assay, disintegration, dissolution, and f_2 similarity analysis further revealed that only selected brands (notably **C** and **E**) demonstrated consistent closeness to the innovator product, suggesting more optimized formulation design and better manufacturing reproducibility. These products likely achieve a balanced interplay between mechanical strength and rapid disintegration, preserving the intended release characteristics of immediate-release metformin formulations. Overall, the observed variability aligns with previous reports from similar markets, which show that many multisource generic products satisfy basic pharmacopoeial standards yet still exhibit measurable differences in chemical content uniformity and in vitro release profiles^{41,42}.

Collectively, these findings emphasize that comprehensive comparative *in vitro* evaluation is essential for assessing therapeutic interchangeability, particularly for widely used drugs such as metformin, where small variations in release behavior may translate into clinically relevant differences in glycemic control.

5. CONCLUSION

This comparative investigation demonstrates that four out of the five evaluated commercial brands of metformin hydrochloride (500 mg) tablets distributed in Khartoum, Sudan, fully comply with standard pharmacopoeial quality attributes. Formulations **A**, **C**, **D**, and **E** met the required specifications for structural strength, weight uniformity, chemical potency, disintegration time, and minimum dissolution thresholds. Mathematical evaluation using the f_2 similarity factor confirmed that the imported generic Brand **C** and the locally manufactured Brand **E** are highly similar to the reference innovator standard, verifying their technical suitability for clinical substitution and potential interchangeability. However, Brand **B** failed to satisfy the required chemical assay margins and the 30-minute **Q** dissolution threshold, while Brand **D** exhibited an accelerated dissolution profile that deviated significantly from the innovator curve.

Based on these outcomes, it is recommended that the National Medicines and Poisons Board (**NMPB**) of Sudan enforce mandatory *in vitro* dissolution profiling and similarity factor (f_2) evaluations as prerequisites for the registration and renewal of all multisource generic products. Furthermore, hospital pharmacies and local procurement authorities should prioritize clinically validated interchangeable generics, such as Brands **C** and **E**, to ensure consistent therapeutic outcomes. Finally, sustained post-marketing surveillance programs must be implemented to monitor the long-term stability and quality of these essential medicines under hot tropical climate conditions, safeguarding patient safety and maintaining effective glycemic control across public health infrastructures.

Statements and Declarations:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data availability:

All data generated or analysed during this study are included in this published article.

Author Contributions Statement:

O.S.: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. A.O. A.: Writing – Review & Editing. A.A. E.: Writing – Review & Editing, Methodology, Investigation, Data. R.A.: Writing – Review & Editing, Methodology, Formal analysis. curation.

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