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RESEARCH ARTICLE

In Vitro Assessment of Pharmaceutical Equivalence of Different Brands of Metformin Hydrochloride Tablets Available in Tertiary Care Hospital in Kathmandu

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Abstract

Diabetes mellitus remains a worldwide health burden, associated with a significant co-morbidity, including heart disease, nerve damage, kidney failure, vision loss, and diminished quality of life. Ensuring therapeutic quality of the drugs is vital to safeguard the treatment efficacy, patient safety, and public health outcomes. Therefore, the aim of the study was to establish the pharmaceutical equivalence of various brands of metformin hydrochloride available in tertiary care hospital in Kathmandu. In this study a systematic quality assessment of weight variation, friability, assay, and related substance impurities were evaluated as per the Indian pharmacopeia (IP 2022). The weight variation test revealed significant mass consistency, within the ±5% accepted range. Friability results were markedly lower than the 1.0% ceiling, falling between 0.041% and 0.286%. All tablets met pharmacopeial disintegration threshold (≤15 min), but times varied significantly (1.57–6.30 min) across the formulations. Assay analysis depicted drug contents ranging from 95.91% to 97.22% of the 500 mg label aligning the pharmacopeial limit. Impurity analysis further validated product`s integrity, with concentrations of dicyandiamide and other unspecified impurities within the threshold's limits. In conclusion, all evaluated metformin brands met the pharmacopeial standards for uniformity, potency, disintegration time, and purity. These results confirm their pharmaceutical equivalence and standard quality, accrediting their substitutability for clinical use within an institutional formulary. This research supplies pivotal quality verification of various brands of the marketed metformin tablets, informing the procurement and formulary management decisions in the tertiary care hospitals.

Keywords: Diabetes mellitus; Co-morbidity; Pharmaceutical equivalence; Metformin hydrochloride; Quality control

Introduction

Diabetes mellitus is a critical global health emergency which impairs insulin function, engendering to increased blood sugar levels. This complication brings a large number of adverse health effects like cardiovascular diseases, neurological disorders, renal diseases, and visual impairment, which are the primary cause of mortality [1, 2]. Over 500 million people worldwide are affected by diabetes mellitus in 2021, as per the data from the International Diabetes Federation (IDF), and projections indicate that the number of people

living with diabetes will rise seriously[3]. This epidemic has extremely profound effect in Nepal. In developing countries like Nepal, patient profile is rapidly shifting that brings an alarming surge in type II diabetes. This rapid increase in diabetes is attributed to physical inactivity, dietary modification as well as urbanization[4, 5]. This growing prevalence of diabetes mellitus poses a major obstacle to the healthcare infrastructure.

Metformin hydrochloride is frontline treatment for controlling type II diabetes. This biguanide drug reduces the blood sugar level by decreasing hepatic glucose production and increasing the muscle glycogenesis as well as insulin sensitization[6]. The metformin is adopted as international benchmark for curing the diabetes and widely spread medication in diabetes as the drug is clinically effective, weight- neutral, glycemically stable, and metabolically favorable[7].

Metformin is procurable in different forms; among them, oral dosage forms are the most potent, as these are more practical and accessible [8]. Within this group, tablets are the most widely used patient compliance dosage form due to their stability, proper administration, correct dosing, and comprehensibility [9]. A drug will be therapeutically potent if the drug content is within the labelled limit, a low dose is sufficient to bring the desired pharmacological effect, and it is easily and readily absorbed in the body[10]. The absence of different contaminants, high potency, and a suitable release mechanism of the active pharmaceutical ingredients are, therefore, the fundamental criteria for an effective drug [11].Different brands of metformin hydrochloride tablets are available in the market with different pricing, which casts doubt upon their quality, therapeutic efficacy. This diversity in pricing brings the questions about the pharmaceutical equivalence of the different brands available in the market[12].

Counterfeit pharmaceuticals, are a major global health emergency, with a higher challenge in developing countries like Nepal [13]. These contraband pharmaceutical products, which include life-sustaining therapy like antimalarial and antivirals, often infiltrate official supply systems and commonly affect high-volume medicines [14]. The consequence of these counterfeit drugs is very serious as they may lead to drug resistance, therapeutic failure, higher mortality rate, and considerable socio-economic harm [15]. In our context, it is noticeable that this problem is scale up, and the researches showed that about one-third of tested drugs were counterfeited[16]. This brings a necessity for the evaluation of pharmaceutical equivalence. *In vitro* analysis of pharmaceutical products such as weight variation, friability testing, disintegration time determination, and assay provides a first-line defense to identify the quality of drugs. To maintain the quality of drugs and fulfill the official compendia, the tested drugs must meet *in vitro* pharmacopeial standards. In contrast, observed deviation in these *in vitro* parameters signifies the therapeutic inequivalence, which influences the clinical outcomes and brings the efficacy and safety issues in clinical trials with possible adverse effects from levels that are too high [17, 18].

This study addresses critical process deviation in quality of marketed drug methodically assessing the *in vitro* performance of different brands of metformin hydrochloride (500mg) available in tertiary care hospitals of Kathmandu. The *in vitro* evaluation in the study includes weight uniformity, friability, disintegration time, assay, and related substances impurity following the standard pharmacopeial protocol, Indian Pharmacopoeia (IP, 2022). The findings of the study will allow evidence based advise to the healthcare professionals in reasonable patient-centered prescription and will provide the data library which will serve as independent post-market surveillance, identifying products needing

scrutiny. The findings of the study also fortify the pharmaceutical industry, imparting Good Manufacturing Practice (GMP) and quality control. Eventually, the study ensures authentic therapeutic quality, trustworthy treatment efficacy, high-reliability patient safety, and public health outcomes for type II diabetes patients in Nepal.

Materials and Methods

Study Design

This study employed an experimental *in vitro* design to evaluate the quality of commercially available metformin hydrochloride tablets from major tertiary care pharmacies within the Kathmandu valley. From a sampling frame of ten centers, seven were selected using simple random sampling. The collected samples underwent comprehensive quality testing, including assessments for weight variation, hardness, friability, disintegration time, assay (drug content), and analysis for related substances (impurities).

Sampling Techniques and Sample Collection

The sampling methodology followed the established "Guidelines for Field Surveys of the Quality of Medicines" by Newton et al [19]. 500 mg metformin hydrochloride tablets were purchased from the previously selected pharmacies, with staff unaware of the study. Sixty tablets of each available brand were obtained in their original packaging from each center. It was noted that each pharmacy stocked only a single brand.

After the collection of samples, brands from the same manufacturer and with identical batch numbers are grouped and assigned the codes as depicted in Table 1. This process yielded four distinct metformin brands for subsequent in-vitro evaluation. Detailed procurement data-including drug name, manufacturer, and country of origin, manufacturing and expiration dates, and batch number were meticulously documented in a standardized spreadsheet. All collected samples were then transported to the Pharmaceutical Chemistry Laboratory at the Department of Pharmacy, Maharajgunj Medical Campus, Tribhuvan University. They were stored under the conditions specified on their product labels until the commencement of laboratory analysis.

Pharmaceutical Performance and Quality Tests

Weight Variation Test

Twenty tablets of each brand were randomly selected to conduct the weight variation test. The average weight of each brand was calculated by measuring the collective weight of selected twenty tablets , and the percentage deviation in weight of each tablet was determined applying the formula presented in equation (1) [20].

$$\frac{[Individual\ wt.\ of\ tablet - Average\ wt.\ of\ tablet]}{Average\ wt.of\ tablet} X\ 100 \ldots \quad (1)$$

Friability Test

The friability of the tablets was estimated with a USP/EP-compliant friabilator by using the ten randomly selected tablets of each brand. In brief, the preweighed samples of each brand were fully dedusted and placed in the rotating drum for 100 revolutions at a speed of 25 revolutions per minute. The samples were taken out after the test, fully dedusted, and reweighed precisely. The percentage friability was calculated by using the formula provided in equation (2) [21].

$$\frac{[Initial\ wt.\ of\ tablet - Final\ wt.\ of\ tablet]}{Initial\ weight\ of\ tablet} X\ 100 \ldots \ldots \ldots \ldots (2)$$

As per pharmacopoeial standards (IP, 2022), for majority of uncoated tablets, a weight loss of not more than 1.0% is generally acceptable.

Disintegration Test

The disintegration test of tablet samples was carried out as per the pharmacopeial guidelines IP, 2022 using validated disintegration test apparatus (Electrolab EDT-08L). In brief, the vessel was first filled with purified water as immersion medium, and thermostatically controlled at 37.5°C by maintaining the water level 15mm below the top of basket. Six tablets of each brand were

placed in each of the six tubes of basket rack, which was then lowered into the immersion medium and the apparatus was started. The time for each tablet to completely disintegrate with no palpable mass residue in the apparatus was noted and acquiescence was proclaimed if all six tablets disintegrated within the allotted fifteen minutes.

Assay Determination

The accurate and precise drug content evaluation of metformin hydrochloride tablet samples was carried out as per the guideline of IP,2022 spectrophotometrically. In brief, twenty metformin hydrochloride tablet samples were weighed and powdered. A powdered sample equivalent to 0.1 gm of metformin hydrochloride was shaken in 70 ml water for 15 minutes, which was then diluted to 100 ml and filtered. The filtrate obtained was then applied for two-stage serial dilution to obtain the final test solution. Firstly, 10ml of the filtrate was diluted to 100ml and then the 10 ml of this diluted solution was further diluted to 100 ml. The content of metformin hydrochloride was calculated at 230 nm taking specific absorbance 798 and distilled water as blank. The experiment was conducted in triplicate, the average metformin hydrochloride content was determined, and was correlated with 95-105% of the label claim.

Related Substances Impurity

Related substance impurities i.e. the primary impurity dicyanamide and other unspecified impurities in metformin hydrochloride tablet samples, were determined based on pharmacopeial guidelines (IP, 2022), which involves high performance chromatographic technique (HPLC) with reference standard for quantification 0.005 mg/ml metformin and 0.001 mg/ml dicyanamide. Briefly, the mobile phase was prepared by dissolving sodium pentane sulphonate (0.87 gm) and sodium chloride (1.2 gm) in HPLC water adjusting the pH at 3.5. The sample solution was prepared by dissolving metformin hydrochloride tablet in the as-prepared mobile phase followed by sonication and filtration. Finally, the concentration of the sample solution was set as 5 mg/ml with dilution. The column containing the strong acid-based cation was maintained at 45°C and the detection was done with a UV detector at a detection wavelength of 218nm by maintaining the flow rate of 1ml/min.

Results and Discussion

Four commercially packaged metformin hydrochloride brands, within their labelled expiry dates, were analyzed as per the guideline of Indian Pharmacopeia (IP, 2022). To ensure traceability, each sample was assigned a unique code. Key details including batch number, manufacture date, and expiry date for each brand are compiled in **Table 1**, providing a complete record of the sourced materials used in this comparative study.

Table 1: Details of the tested metformin tablet samples.

Assigned Code	Mfg. Date	Exp. date	Source of Supply
ST-1	12/ 2023	11/ 2025	Hospital tender
ST-2	10/ 2023	09/ 2026	Hospital tender
ST-3	11/ 2023	10/ 2025	Hospital tender
ST-4	05/ 2023	08/ 2025	Hospital tender

Weight Variation Test

The results of the weight variation test confirmed that all four metformin brands (ST-1 to ST-4) complied with the pharmacopoeial specification, as no tablet deviated beyond the permissible ±5% limit from its respective batch average as depicted in **Table 2**. The average tablet weights, however, exhibited significant

inter-brand variation, ranging from 591.93 mg (ST-4) to 673.38 mg (ST-1). This compliance demonstrates effective in-process control and consistent powder filling during manufacturing for each individual product [22]. The substantial difference in mean mass, exceeding 80 mg between the highest and lowest, is a critical finding. It directly reflects considerable differences in the excipient composition, such as diluents and binders used by various manufacturers to formulate a standard metformin dose [23]. While this confirms pharmaceutical equivalence in terms of active ingredient content and basic physical uniformity, it highlights a lack of pharmaceutical identity.

Table 2: The weight variation test results for the metformin hydrochloride tablet samples.

Brand	Total weight (gm)	Average weight (mg)	Average weight ±5% i.e. limit(mg)	Tablets deviating Limit
ST-1	13.4675	673.375	639.70-707.04	Nil
ST-2	13.4382	671.91	638.31-705.50	Nil
ST-3	13.0588	652.94	620.29-685.58	Nil
ST-4	11.8386	591.93	562.33-621.52	Nil

Friability Test

The friability test results demonstrated that all four metformin brands exhibited weight loss significantly below the 1.0% pharmacopoeial limit, with values of 0.179% (ST-1), 0.286% (ST-2), 0.041% (ST-3), and 0.188% (ST-4) as depicted in **Table 3**. This confirms that each formulation possesses sufficient mechanical strength to resist abrasion during handling and transport. The notable seven-fold variation in results, however, reveals critical formulation differences. Although all products are compliant, the range in friability highlights disparities in excipient composition and manufacturing process control [24]. These physical variations, while not directly indicative of drug efficacy, influence product durability, packaging requirements, and patient perception of quality, emphasizing that pharmaceutical equivalence does not guarantee identical physical performance characteristics [25].

Table 3: Friability test results for metformin hydrochloride tablets.

Brand	Initial weight (W1) gm	Final weight (W2) gm	% Weight Loss
ST-1	6.7823	6.7701	0.179
ST-2	6.7675	6.7481	0.286
ST-3	6.5410	6.5383	0.041
ST-4	5.9013	5.8902	0.188

Disintegration Test

All tablet brands satisfied the pharmacopeial requirement (IP, 2022) of ≤15 minutes for disintegration as depicted in **Table 4**.

Table 4: *In vitro* disintegration test results for the metformin hydrochloride tablet.

Brand	Disintegration Time/minutes
ST-1	1.57
ST-2	6.30
ST-3	5.8
ST-4	4.6

A marked variation in disintegration times was nevertheless recorded, ranging from a rapid 1.57 minutes for ST-1 to a comparatively slower 6.30 minutes for ST-2, with ST-3 and ST-4 displaying intermediate values. The statistically significant differences ($p < 0.05$) indicate probable formulation and manufacturing disparities, including the excipient composition and compression parameters used [26]. The

notably swift disintegration of ST-1 suggests an optimized design that could promote earlier drug release in vivo [27]. Since disintegration is a pivotal precursor to dissolution and systemic absorption [28], these findings imply that therapeutic equivalence among the brands cannot be assumed based on compliance alone.

Assay Test

All four metformin brands met the pharmacopeial assay specification (95-105% of label claim), with average potencies between 95.91% and 97.22% as depicted in **Table 5.**

Table 5: Assay results for metformin hydrochloride tablet brands.

Brand	Sample 1	Sample 2	Average Content
ST-1	479.385 mg/tab* (95.87%)	492.875 mg/tab* (98.57%)	486.130 mg/tab* (97.22%)
ST-2	481.875 mg/tab* (96.37%)	489.639 mg/tab* (97.92%)	485.757 mg/tab* (97.15%)
ST-3	465.965 mg/tab* (93.19%)	464.588 mg/tab* (95.91%)	465.276 mg/tab* (95.91%)
ST-4	476.039 mg/tab* (95.20%)	483.354 mg/tab* (96.67%)	479.696 mg/tab* (95.93%)

*Mean of 20 samples

Brand ST-1 showed the highest and most uniform content (97.22%). Notably, Brand ST-3 displayed significant sample-to-sample variability, with individual results of 93.19% and 95.91%. While its final average complied, this wide range suggests inconsistencies in the powder blending or granulation process, leading to poor content uniformity within the batch [29]. In contrast, the tighter results for ST-1, ST-2, and ST-4 reflect more precise manufacturing control. The critical finding is that compliance with an average potency standard does not guarantee dose uniformity in every tablet [30]. For a chronic medication like metformin, such intra-batch variability could lead to inconsistent daily dosing, potentially affecting long-term therapeutic outcomes and underscoring the need for rigorous process validation beyond final assay compliance [31].

Related Substances Impurity

The related substances analysis, carried out following the guidelines of Indian Pharmacopoeia (IP) 2022 demonstrated that all four metformin hydrochloride brands corroborated with the specified impurity limits, confirming acceptable purity profiles (**Table 6**). Dicyandiamide, which is a known process-related impurity [32] with a stringent maximum limit of 0.02%, was identified in three brands including ST-1 (0.0042%), ST-3 (0.0052%), and ST-4 (0.0050%). In contrast, dicyandiamide was not detected in ST-2, which may reflect differences in the manufacturing process or the effectiveness of purification steps employed by this manufacturer. In addition, an unidentified impurity was observed in all samples, with levels ranging from 0.0023% in ST-1 to 0.053% in ST-4. All values remained well below the IP-specified acceptance limit of 0.1% for unspecified impurities, indicating satisfactory control of related substances and overall product quality. This compliance suggests the effectiveness of implemented Good Manufacturing Practices (GMP) to control synthesis and purification processes, thereby producing APIs of high purity. The uniformity, low-level presence of the secondary impurity across entire brands indicates that it may represent a common minor degradation product or a residual synthetic intermediate that is inherently difficult to eliminate entirely [33]. The absence of dicyandiamide in ST-2 brands reflects formulation diversity and the universal compliance is a positive indication of

the regulatory control, which effectively filter out products with critical contamination problems [34].

Table 6: Related substances impurity analysis of various brands against IP 2022 specifications.

Brand	Peak due to Dicyandiamide	Other Secondary peak	Compliance
ST-1	Detected: 0.0042%	Detected: 0.0023% Detected: 0.050%	Complies
ST-2	Not Detected	Detected: 0.019% Detected: 0.0425%	Complies
ST-3	Detected: 0.0052%	Detected: 0.017% Detected: 0.043%	Complies
ST-4	Detected: 0.0050%	Detected: 0.015% Detected: 0.053%	Complies

Conclusions

In conclusion, all evaluated brands complied with pharmacopeia specifications for uniformity, potency, disintegration, and purity, providing empirical evidence of acceptable pharmaceutical quality. In addition, related substances analysis confirmed the chemical integrity of the formulations, as levels of dicyandiamide and other unspecified impurities were substantially below the limits prescribed by the Indian Pharmacopoeia (2022). Collectively, these findings support the pharmaceutical equivalence of the assessed products and indicate their suitability for inclusion within a hospital formulary, while acknowledging formulation-related differences that warrants further dissolution or in-vivo evaluation.

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Author's contribution statement

S. Timsina: Conceptualization, Methodology, Investigation, **R. Adhikari:** Methodology, **P. Prasad:** Investigation, Supervision, **S. Thapaliya:** Methodology, Analysis, Investigation **A. Budthapa:** Visualization, Supervision, **S. K. Sah:** Formal analysis, Investigation, **M. K. Joshi:** Conceptualization, Formal analysis, Writing- review &editing, Supervision, **S. Pandeya:** Conceptualization, Writing- review& editing, Supervision

Conflict of interest

The authors do not have any conflict of interest related to this research work.

Data availability statement

The datasets generated during this study are available from the corresponding author on reasonable request.

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