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Herb–Drug Interaction and Antidiabetic Drug Development: A Spectroscopic and Pharmacokinetics Investigation of *Polyalthia Longifolia* Versus Metformin

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ABSTRACT

Diabetes mellitus is a chronic metabolic condition characterized by consistently high blood sugar levels, resulting from problems with insulin production, insulin function, or both. Metformin remains the most widely recommended first-line treatment for type 2 diabetes because of its proven effectiveness, good safety profile, and ability to improve the body's response to insulin. Despite its benefits, many diabetic patients now combine metformin with herbal remedies, such as *Polyalthia longifolia*, in hopes of gaining additional health advantages. While this practice is increasingly common, it also raises important concerns about possible herb–drug interactions, especially since there is limited scientific evidence on how *Polyalthia longifolia* may affect the pharmaceutical performance of metformin. Understanding these interactions is essential to ensure safe co-administration, preserve therapeutic effectiveness, and prevent unwanted changes in drug absorption or availability. In this study, the effect of methanolic extract of *Polyalthia longifolia* on the in-vitro dissolution profile of different brands of metformin tablets was investigated. The selected metformin brands were first evaluated for key physicochemical properties according to pharmacopeia standards. Findings showed that all brands met the required quality specifications, including friability values below 1%, weight variation within ±5%, disintegration times under 15 minutes, and hardness values ranging from 4–10 kg/F. These results indicate that the tablets possessed satisfactory quality, strength, and formulation stability. Further phytochemical screening of the plant extract revealed the presence of important bioactive compounds such as alkaloids, flavonoids, saponins, terpenoids, steroids, and cardiac glycosides, all of which may influence drug dissolution and absorption. To assess potential interactions, dissolution studies were conducted in phosphate buffer (pH 6.8) to simulate intestinal conditions, both in the absence and presence of the plant extract. The results demonstrated that *Polyalthia longifolia* extract significantly increased the apparent dissolution rate of metformin, with some tablet brands achieving complete drug release of up to 100%. This increase may be due to physicochemical interactions between the extract and the drug, enhanced solubilization, or possible analytical interference from phytochemical constituents present in the extract. In summary, methanolic extract of *Polyalthia longifolia* significantly altered the dissolution behavior of metformin tablets, suggesting a potential herb–drug interaction that may influence the drug's bioavailability and therapeutic response. These findings highlight the importance of exercising caution when *Polyalthia longifolia* is used alongside metformin and reinforce the need for further in-vivo studies to determine the real clinical significance of this interaction.

Keywords: *Polyalthia longifolia*; metformin; drug-herb interaction; bioavailability; hypoglycemia.

1.0 INTRODUCTION

Medicinal plants have been used since antiquity as sources of food, flavoring agents, and therapeutic remedies. Long before the development of modern synthetic pharmaceuticals, humans relied extensively on plant-based preparations for the prevention and treatment of diseases. Even in the present era, herbal medicines remain an integral component of healthcare systems worldwide, particularly in developing countries where access to and affordability of conventional medicines may be limited. The World Health Organization estimates that approximately 70–80% of the global population relies on traditional medicine, largely derived from plants, for primary healthcare needs (WHO, 2022).

Plants exert their medicinal effects largely through secondary metabolites such as alkaloids, flavonoids, phenolic compounds, terpenoids, tannins, and glycosides. These bioactive constituents have been shown to possess diverse pharmacological properties, including antioxidant, antimicrobial, anti-inflammatory,

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anticancer, and antidiabetic activities. Recent research has further emphasized the role of plant-derived phytochemicals in modulating metabolic pathways, enzyme activity, and oxidative stress, which are central to the pathophysiology of chronic diseases such as diabetes mellitus (Kumar *et al.*, 2023; Martins *et al.*, 2024).

Polyalthia longifolia (family: *Annonaceae*) is a medicinal plant widely distributed in tropical regions and commonly used in traditional medicine. Various parts of the plant, particularly the leaves and stem bark, have been reported to exhibit significant biological activities. Contemporary studies have demonstrated that methanolic extracts of *P. longifolia* leaves are rich in phenolic and flavonoid compounds and exhibit strong antioxidant and in vitro antidiabetic activities, including α-glucosidase inhibition and antiglycation effects (Sivakumar *et al.*, 2025). *P. longifolia* holds a significant place in Indian traditional medicine, where it is commonly employed for several medicinal purposes, including the treatment of hypertension, management of intestinal parasites, regulation of glycemia, and as an anti-inflammatory remedy. Phytochemical investigations have reported the presence of various constituents, mainly terpenes (clerodane diterpenes), tannins, polyphenols, and aporphine alkaloids. These mechanisms are relevant in controlling postprandial hyperglycemia and delaying the progression of diabetic complications.

Diabetes mellitus is a long-term metabolic condition marked by consistently elevated blood glucose levels due to impaired insulin production, reduced insulin effectiveness, or a combination of both. Type 2 diabetes mellitus accounts for the majority of diabetes cases globally and is associated with significant morbidity, mortality, and economic burden. Metformin, a biguanide oral hypoglycemic agent, remains the first-line pharmacological therapy for the management of type 2 diabetes due to its efficacy, safety profile, and ability to reduce hepatic glucose production and improve insulin sensitivity (Foretz *et al.*, 2023). Metformin is marketed by numerous pharmaceutical companies under different brand names, often with variations in excipients and formulation characteristics, which may affect dissolution behavior and drug performance in vitro.

The concurrent use of herbal products and conventional antidiabetic drugs has become increasingly common among patients with diabetes. While herbal medicines are often perceived as "natural" and therefore safe, scientific evidence indicates that herbal–drug interactions can occur and may significantly influence drug behavior. These interactions may be synergistic, antagonistic, or neutral and can affect drug stability, dissolution, absorption, and bioavailability. Recent reviews have highlighted the growing concern over herb–metformin interactions, emphasizing the need for systematic experimental studies to evaluate potential physicochemical and biochemical interactions, particularly at the in vitro level (Al-Asmari *et al*., 2022; Nugraha *et al.*, 2022).

Despite increasing evidence supporting the antidiabetic potential of *Polyalthia longifolia*, there is a notable lack of data regarding its interaction with standard antidiabetic drugs such as metformin. Furthermore, limited attention has been given to the possibility that different commercial brands of metformin may respond differently when exposed to herbal extracts due to formulation-related differences. Understanding such interactions is essential to ensure the safe and effective use of herbal remedies alongside conventional antidiabetic therapy.

Therefore, this study is designed to investigate the in vitro effect of the methanolic extract of *Polyalthia longifolia* on different brands of metformin. The findings of this research will provide valuable baseline information on potential herb–drug interactions, contribute to safer integrative diabetes management practices, and serve as a foundation for future in vivo and clinical studies

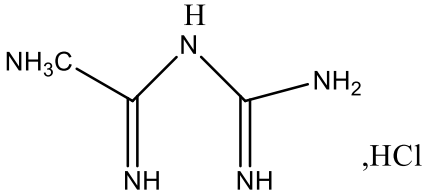

Figure 1: Structure of metformin Hydrochloride

Figure 2: Authenticated leaves of polyalthia longifolia

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2.0 MATERIALS AND METHODS

2.1 Materials

2.1.1 Reagents and Equipment

Beaker, 800ml, 100 ml, 50 ml (Pyrex, England), Conical flask, 100 ml, 50 ml (Pyrex, England) Measuring cylinder, 1000 ml, 100 ml, 10 ml (Pyrex, England), Volumetric flask, 100 ml,50 ml, 25 ml (Pyrex, England),Whatman filter paper (Swastik Scientific Company, UK),Spatula, Mortar and pestle, Spatula, Foil paper, Quartz cuvette, Stop watch, Test tube rack Analytical balance (AR223CN, OHAUS Corporation Pine Brook, NJ, USA),pH meter HI9313-5 (Hanna Instruments, U.S.)Rotary shaker M/C SR. No RS 693 (Ambala Cantt Ambala-Cantt Haryana, India), Oven model DEG-9330 (Yamato Scientific Co. Ltd, Japan), Digital friability test apparatus (Model 902), Up disintegration test apparatus (Model 1901), Dissolution test apparatus (Hindustan Apparatus Management company, India), UV-visible spectrophotometer (UV752, pec medical USA), Monsanto hardness tester. Distilled water, Solution of potassium dihydrogen orthophosphate (0.68% w/v),0.1N Sodium hydroxide, Methanol (Loba Chemi Pvt. Ltd., India).

2.2 Methods

2.2.1 Sampling of Metformin Hydrochloride Tablets (500 mg)

The type and brand of metformin (500 mg) used in the study were obtained randomly from Pharmacies within Kaduna metropolis, Kawo and Sabon Tasha, Kaduna State and presented as brands A-D in Table 1.

2.2.2 Collection and identification of plant material (*Polyalthia longifolia*)

Polyalthia longifolia leaves were collected from Ungwan Rimi, Kaduna State during the raining season on the 25th of May, 2025.The plant was identified and authenticated by a taxonomist, Mallam U.S Gallah and a voucher number was assigned KASU/BSH/1213 and sample specimen was archived in the Herbarium of Department of Pharmacognosy and Drug Development of the Faculty of pharmaceutical Sciences, Kaduna State University, Nigeria

2.2.3 Herbal Preparation

Polyalthia longifolia leaves were cleaned, dehusked, and chopped into little pieces. They were subsequently air dried for 18 days at room temperature at the research laboratory. They were then pounded and pulverized into a fine powder with a mortar and pestle before being stored.

2.2.4 Extraction

The fine powder (134.6g) of *Polyalthia longifolia* leaves was extracted using the cold maceration method for 72 hours with one liter of ethanol. (USP 46–NF 41, 2023). Following repeated weighing, the extract was filtered and allowed to evaporate to dryness in a Buchner funnel, yielding a constant yield and a percentage yield of 6.54%, indicated that the ethanol has been completely removed from the extract.

2.2.5 Identification of metformin hydrochloride Tablets by FTIR

The various tablets as well as the reference standard were identified by the BP specified method. This involved powdering the tablets and a small fraction of the powder placed on an already cleaned glass slide attached to an FTIR equipment for analysis.

2.2.6 Evaluation of Physicochemical Parameters of metformin hydrochloride Tablets

The different brands of metformin tablets were subjected to different physicochemical tests, namely: friability, disintegration, dissolution, hardness, thickness and diameter, and weight uniformity tests in accordance to standard compendia (USP 46–NF 41, 2023).

2.2.6.1 Weight variation

Twenty (20) metformin tablets of each brand were weighed individually using an analytical weighing balance and their arithmetic mean weighed and relative standard deviation determined. Result was calculated using the formula below;

$$\text{Percentage of ethanol removed} = \frac{\text{Total loss of weight}}{\text{Weight of crude powder}}$$

$$\%\ \text{standard deviation} = \frac{\text{weight of tablets} - \text{average weight of tablets}}{\text{Average weight}} * 100$$

2.2.6.2 Friability Test

From the various brands of metformin, 10 tablets were brushed to remove surface powder, then weighed accurately, the tablets were then placed in “Digital friability test apparatus (model 9021)”. The tablets were rotated in the drum for 4 minutes at a speed of 25 revolutions per minute. Afterward, they were taken out, cleaned of dust, and weighed again. Friability was then calculated using the formula:

$$\text{Friability} = \frac{W1 - W2}{W2} * 100$$

where: W1 = initial weight and W2 = final weight

2.2.6.3 Drug Content Assay

Twenty tablets were randomly selected and crushed into a fine powder. An amount of the powder equivalent to 500 mg of metformin was transferred into a 100 mL volumetric flask, dissolved in 50 mL of 0.1 N HCl, and then diluted to volume with the same solvent. The mixture was subsequently filtered using Whatman filter paper. A 1.0 mL aliquot of the filtrate was further diluted to 100 mL in another volumetric flask and made up to the mark. The absorbance of the final solution was measured at a maximum wavelength of 233 nm using a UV–visible spectrophotometer. A calibration curve of absorbance versus metformin concentration was then constructed. The assay procedure was adapted from the method described by (Ganesh *et al.*, 2020).

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2.2.6.4 Disintegration time

From the various brands of metformin, 6 tablets were randomly selected and placed in the" Up disintegration test apparatus (model 1901)" the disintegration time for the 6 tablets in water at 37±0.5 ℃ were determined, to comply with USP standards all the tablets had to disintegrate and all particles passed through the mesh screens. Therefore, the time taken to disintegrate was recorded.

2.2.7 Dissolution test of metformin hydrochloride tablets alone

The dissolution profile of metformin tablets was evaluated in line with more recent pharmacopoeia guidance (e.g., British Pharmacopoeia) using a type II dissolution apparatus (paddle method). The test was conducted at 100 rpm and a temperature of 37 ± 0.5 °C on six tablets from each brand. A 900 mL volume of 0.68% w/v potassium dihydrogen orthophosphate buffer, adjusted to pH 6.8 with 0.2 M sodium hydroxide, served as the dissolution medium. At predetermined intervals (5, 10, 20, 30, 45, and 60 minutes), 10 mL samples were withdrawn and filtered, with an equal volume of fresh medium added to maintain sink conditions. The absorbance of the filtered samples was then measured at a maximum wavelength of 232 nm using a UV–visible spectrophotometer.

2.2.8 Dissolution Study of metformin hydrochloride in the Presence of *Polytalthia longifolia*

Once the dissolution medium was heated to 37 ± 0.5 °C, 1 g of *Polyalthia longifolia* extract was introduced into the vessels containing 0.68% w/v potassium dihydrogen orthophosphate solution, and the mixture was stirred using a glass rod. The dissolution vessel was immediately run at 50 rpm for 15 minutes after one metformin tablet was added. To track the dissolution, five sampling intervals were established: 10, 20, 30, 40, and 50 minutes. Using a syringe, a 10 ml sample was taken at each sampling location between the top of the spinning sample and the dissolution medium's surface and the entire dissolution test was conducted with the vessel covered. Before being analyzed using UV spectrophotometry at 232 nm, the samples were filtered via a membrane filter, and each sample's absorbance was calculated.

2.2.9 Data Analysis

Data obtained were treated using the ORIGIN graphing and scientific analysis software program, Microsoft Excel 2007 and Windows SPSS Version 22. Comparison and statistical significance were determined by a one-way analysis of variance (ANOVA). All data were analyzed at a 95 % confidence interval ($P < 0.05$).

3.0 RESULTS

Table 1: Showing the description of metformin hydrochloride tablets obtained;

Brand	Brand A	Brand B	Brand C	Brand D
Batch No.	CC077 14	23100 8	230806 9	FPC0805 24
Nafdac No.	04-0810	B4-9596	C4-0303	04-6426
Production Date	07/2023	10/2023	08/2023	03/2024
Expiration Date	06/2026	09/2026	07/2026	02/2027

Fourier Transform Infrared Spectroscopy of metformin tablets represented as brands A, B, C and D respectively and their spectra were presented in figures (3- 6) identified/confirmed by FTIR.

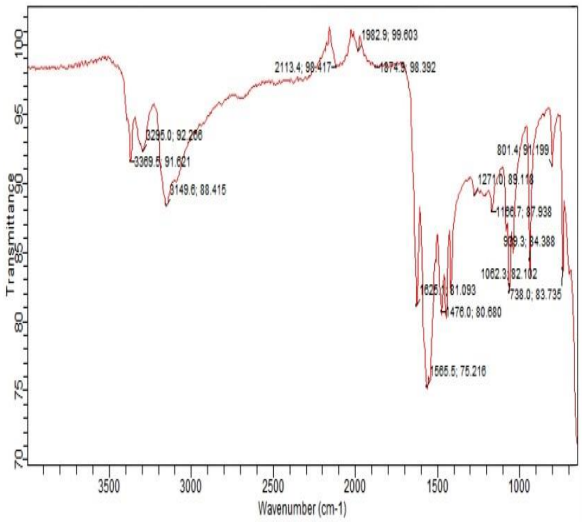

Figure 3: FTIR spectra of brand A

n

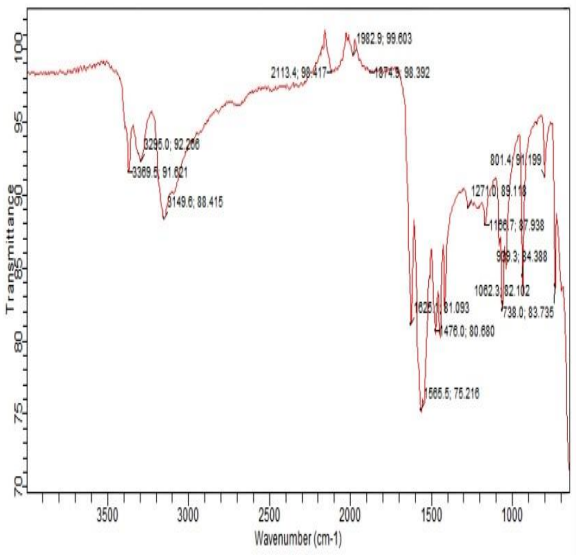

Figure 4: FTIR spectra of brand B

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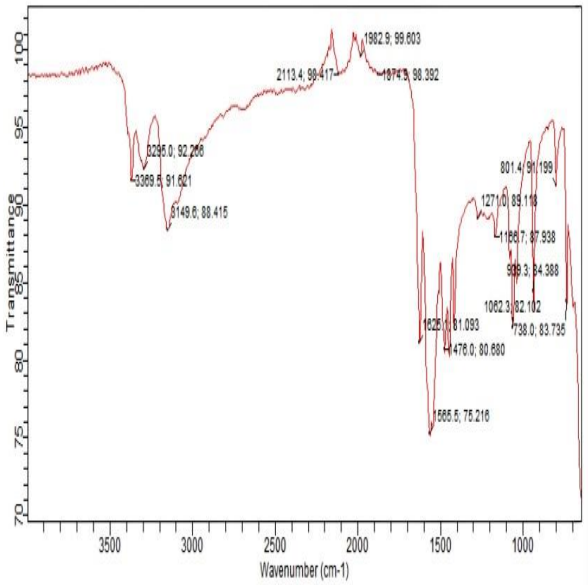

Figure 5: FTIR spectra of brand C

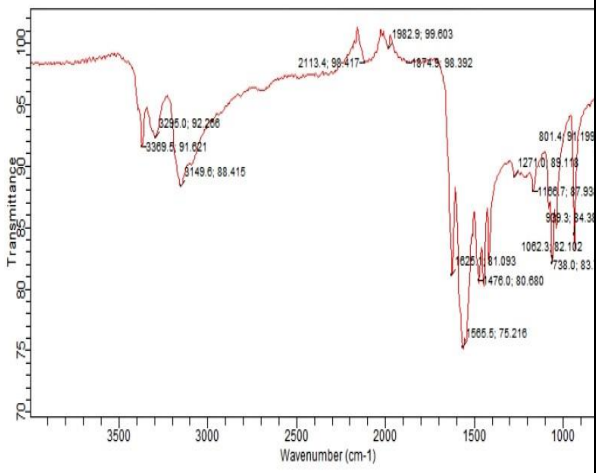

Figure 6: FTIR spectra of brand D

Table 2: The % Friability of Metformin tablet brands A, B, C and D (n=10)

S/N	Brand A (%)	Brand B (%)	Brand C (%)	Brand D (%)
1	0.02	0.17	0.00	0.15
2	0.00	0.29	0.00	0.12
3	0.03	0.20	0.05	0.04
4	0.02	0.48	0.06	0.15
5	0.00	0.14	0.06	0.04
6	0.03	0.51	0.00	0.25
7	0.05	0.27	0.07	0.05
8	0.04	0.00	0.00	0.20
9	0.00	0.08	0.09	0.19
10	0.00	1.20	0.05	0.35
Mean± SD	0.019±0.019	0.034±-0.34	0.038±0.035	0.154±0.10

Table 3: Weight variation of Metformin Brands (A, B, C and D)

S/N	Brand A (% SD)	Brand B (% SD)	Brand C (% SD)	Brand D (% SD)
1	+2.92	+1.50	-1.06	-0.46
2	-0.51	+3.14	0.17	-0.31
3	+1.20	-3.49	+2.47	+3.52
4	-5.66	-2.66	+0.71	-0.31
5	+2.92	+1.50	+4.24	-1.07
6	+2.92	-0.17	-1.94	+0.46
7	-2.23	-3.49	-1.06	-0.31
8	+2.92	-7.32	-2.82	-0.31
9	-3.95	-0.17	+0.71	+0.46
10	-0.51	-0.17	+4.36	+3.52

Table 4: Hardness Test of Brands A, B, C and D of Metformin Tablets in kg/F (n=10)

Tablet No.	Brand A	Brand B	Brand C	Brand D
1	8.0	5.5	7.5	6.4
2	7.8	5.5	7.6	6.0
3	8.3	5.7	7.0	6.8
4	8.6	5.2	7.5	6.4
5	8.0	5.7	7.0	6.8
6	8.3	5.3	7.5	6.9
7	7.5	5.5	7.0	6.8
8	8.5	5.3	7.5	6.4
9	8.0	5.2	7.6	6.8
10	8.5	5.5	7.0	6.0
Mean ± SD	8.15±0.35	5.44±0.18	7.32±0.28	6.53±0.34

Oral tablets possess a hardness range of 4 to 10 kg according to non-official USP specifications (USP,2023)

Table 5: Disintegration test for Metformin tablet brands A, B, C and D (n=6)

Brand	Disintegration (min)
A	6.23±0.13
B	2.62±0.26
C	5.63±0.37
D	3.80±0.48

Acceptable range: Should not exceed 15 minutes (BP, 2023)

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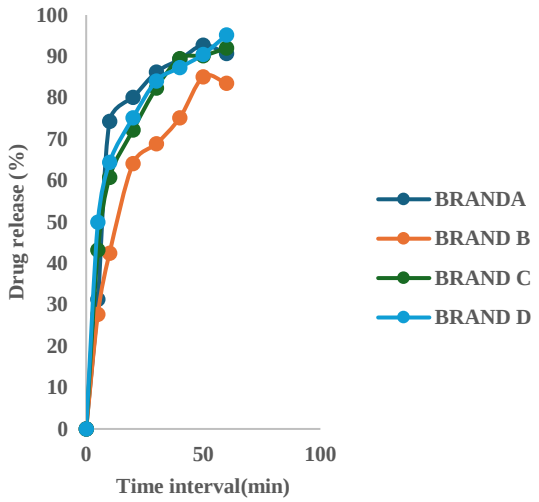

Figure 7: Drug release profile of different brands of Metformin alone

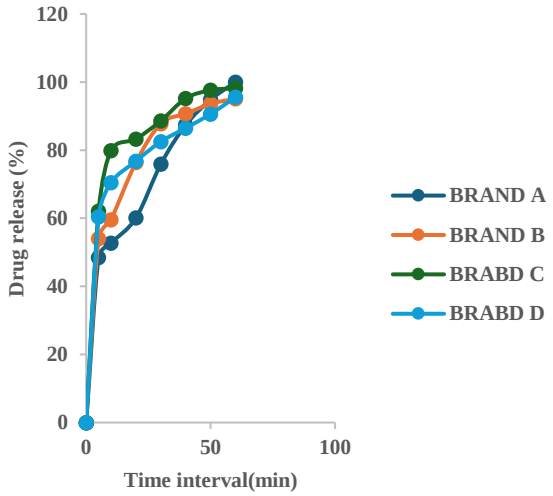

Figure 8: Drug release profile of different brands of Metformin with extract.

4.0 DISCUSIONS

4.1FTIR Spectra for the Brands of Metformin Tablets

The brands used for the analysis have been represented as brands A, B, C and D respectively and were identified/confirmed by FTIR.From the results of Fourier transform infrared (FTIR) spectra of brand A-D figures 3-6, it can be deduced that all the brands were identified as metformin. Absorption bands of the functional groups arise from stretching and deformation vibrations (4000 – 1400 cm-1) and a close fingerprint (1400 – 900 cm-1). All the Brands were suspected to have a spectrum close to that of the monograph reference standard, thus have passed the identification test and are identified as metformin. (BP, 2023).

4.2 Weight variation of metformin tablets

The weight variation test of the four brands of metformin tablets revealed that none of the brands deviated from the official limit (±5%), revealed that , they met the BP requirement and, as such, passed the weight variation test(Table-3). Since it is not a confirmatory test, weight variation provides a general indication of content consistency.

4.3 Hardness of metformin tablets

The mechanical integrity of the four metformin brands (A, B, C, and D) is detailed in Table 4. Tablet hardness is an important quality control parameter that determines the ability of tablets to withstand mechanical shock and stress during manufacturing, packaging, transportation, and handling by patients. According to non-official USP specifications, conventional oral tablets should generally possess a hardness range of 4–10 kg/f to ensure adequate mechanical strength without affecting disintegration and dissolution properties (USP, 2023).

The mean hardness values obtained for Brands A, B, C, and D (Table-4), were 8.15 ± 0.35 kg/f, 5.44 ± 0.18 kg/f, 7.32 ± 0.28 kg/f, and 6.53 ± 0.34 kg/f, respectively. All the brands exhibited hardness values above the minimum acceptable crushing strength of 4 kg/f, indicating satisfactory mechanical resistance and adequate ability to withstand fracture during handling and transportation. Brand A showed the highest hardness value, while Brand B had the lowest; however, all brands still fell within the acceptable range for conventional tablets. The relatively low standard deviation values observed among the brands indicate uniformity in tablet compression and consistency during production. These findings suggest that the manufacturing processes for all the evaluated brands were adequately controlled to produce tablets with acceptable mechanical strength. Adequate hardness is essential because excessively hard tablets may delay disintegration and dissolution, whereas very soft tablets may break easily during handling. Therefore, the hardness profiles observed for all the metformin tablet brands indicate good tablet quality and compliance with pharmacopeia expectations (Sougi *et al.*, 2021; USP, 2023).

4.4 Friability test for the four (4) brands of metformin tablets

The friability test is a key quality control parameter used to evaluate the ability of tablets to resist abrasion and mechanical stress during handling, packaging, and transportation. In accordance with current pharmacopoeia standards such as the British Pharmacopoeia and United States Pharmacopeia, a friability value of not more than 1% is generally considered acceptable for conventional uncoated tablets.

Based on the results in Table 2, all the metformin tablet brands (A, B, C, and D) complied with the pharmacopoeia requirement, as their mean friability values were below the 1% limit. Brand A exhibited the

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lowest mean friability (0.019 ± 0.019%), indicating excellent mechanical strength and a high resistance to abrasion. Brand C (0.038 ± 0.035%) also showed good tablet integrity with minimal weight loss. Brand B demonstrated noticeable variability in its results, including a high friability value of 1.20% in one trial. Although the overall mean remained within acceptable limits, this inconsistency may suggest variability in manufacturing conditions such as compression force or granule binding efficiency.

Brand D recorded the highest mean friability (0.154 ± 0.10%), indicating relatively lower resistance to mechanical stress compared to the other brands. However, its values were still well within the acceptable pharmacopeia range. In summary, all the brands met the official requirements for friability, confirming adequate mechanical strength. However, Brands A and C showed superior performance, while Brands B and D exhibited greater variability, which may warrant further quality consistency checks in line with pharmacopoeia recommendations.

4.5 Disintegration test for the metformin tablets

All brands of metformin hydrochloride evaluated had disintegration times that did not exceed the official compendium's 15-minute limit are presented in Table 5, proving that all five brands of metformin tablets had disintegration times. Based on the results obtained, the four brands of metformin used in the test had a disintegration time of 5.34, 7.36, 5.34, 7.82, and 7.40 for brands A, B, C and D respectively.

4.6 Assay of metformin tablets

The chemical content (assay) values of metformin tablets fell within the monograph specifications (95-105%). Brand A of the metformin tablets used had a of value 96.6%, hence has qualitatively passed the assay test and was confirmed to have percentage content in line with that specified in the monograph.

4.7 In vitro-Dissolution profile of the metformin tablets

The different brands of metformin hydrochloride tablets dissolved 75% of the total tablet within 45 minutes, as presented in figure 7 which shows that all four brands of metformin tablets did not deviate (Alfadl *et al.*, 2021). Dissolution and bioavailability of drugs can be influenced by the formulation elements and drug manufacturing procedures used. Tablets made using dry, wet granulation, or direct compression, may behave differently in test tubes and living things. These elements directly influence the breakdown of dosage forms in gastrointestinal fluids, which in turn influences drug absorption.

4.8 Dissolution Study of metformin hydrochloride in the Presence of *polytalthia longifolia*

The *in vitro* dissolution study demonstrated that *Polyalthia longifolia* extract influenced the release behaviour of metformin tablets across all tested brands (A–D) (Figure 8). Although differences were observed in the rate of drug release, all formulations showed a gradual increase in dissolution over time, with drug release ranging from approximately 95.1% to 100% after 60 minutes. This suggests that the presence of the herbal extract did not prevent the complete release of metformin from the tablets.

Variations were mainly observed during the early stages of dissolution. Brand A showed a slower initial release, with 48.5% of the drug released at 5 minutes, but later achieved complete dissolution at 60 minutes. Brand B displayed a slightly faster initial release (54.0% at 5 minutes), although its final dissolution was lower than the other brands at 95.1%. Brand C demonstrated the most consistent dissolution pattern, with rapid drug release at 10 minutes (79.9%) and a final dissolution value of 98.2%. Brand D showed a moderate and steady release profile throughout the study, reaching 95.6% dissolution at 60 minutes.

The differences observed among the brands may be related to interactions between components of *Polyalthia longifolia* and the drug formulations. Bioactive constituents such as flavonoids, alkaloids, and phenolic compounds present in the extract may influence factors such as drug solubility, wetting, and diffusion, thereby affecting the dissolution process. In addition, trace elements in the extract may contribute to slight changes in drug–medium interactions (Begum *et al*., 2021; Kumar & Singh, 2023). Despite these variations, all formulations met acceptable dissolution requirements, indicating that the interaction was relatively mild and did not interfere with the overall release of metformin. However, the differences in dissolution rate suggest that the extract may influence how quickly the drug becomes available for absorption. This finding points to a possible herb–drug interaction between metformin and *Polyalthia longifolia*, emphasizing the need for further *in vivo* studies to determine whether these effects could influence the therapeutic performance of metformin in clinical use.

5.0 CONCLUSION

The results of this in-vitro study evaluated metformin brands (A–D) met key pharmacopoeia standards (British Pharmacopoeia; United States Pharmacopeia), confirming good quality, proper drug content, and reliable performance. While minor variations were observed, all results remained within acceptable limits. However, *Polyalthia longifolia* extract affected metformin dissolution, indicating a possible herb–drug interaction and the need for caution and further in vivo studies.

6.0 CONFLICTS OF INTEREST

All authors in this manuscript do not have any conflicts of interest to declare.

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