



**MODULATION OF METFORMIN DISSOLUTION KINETICS BY
MANGIFERA INDICA SEED ETHANOLIC EXTRACT: AN IN-VITRO
HERB-DRUG INTERACTION STUDY**

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Abstract

Metformin is an oral hypoglycaemic agent and the drug of choice for the management of type 2 diabetes mellitus. Mangifera indica seed is a natural product used in traditional medicine in West and Central Africa and is widely used in Nigeria for the treatment of diabetes mellitus. This study investigated the effect of Mangifera indica seed ethanolic extract on the in vitro dissolution profile of metformin hydrochloride tablets. Five brands of metformin hydrochloride tablets (500 mg) were randomly selected from Kaduna metropolis, Kaduna State. Tablet authenticity was confirmed using Fourier transform infrared (FTIR) spectroscopy, and physicochemical properties were evaluated using official compendial methods. All brands complied with approved in vitro dissolution and disintegration specifications. The dissolution results showed that 96.48% of metformin was released at 45 minutes in the absence of the extract, compared with 53.63% in the presence of Mangifera indica seed ethanolic extract. These findings indicate that Mangifera indica seed ethanolic extract significantly alters the dissolution profile of metformin tablets. Therefore, concomitant administration of Mangifera indica and metformin hydrochloride tablets may reduce metformin bioavailability and potentially lead to therapeutic failure.

Keywords: Herb-drug interaction; *In vitro* dissolution kinetics; *Mangifera indica* seed extract; Metformin hydrochloride.

Introduction

Plants are the oldest medicines known to humankind. Ethnobotanical reports indicate that approximately 800 plants may possess antidiabetic potential (Rover *et al.*, 2002). Medicinal foods are widely prescribed even when their biologically active compounds are unknown, due to their perceived safety, effectiveness, and availability (Warjeet, 2011).

Diabetes mellitus and its complications constitute a major global health problem (ADA, 2014). It has become one of the leading causes of morbidity and mortality worldwide, alongside cancer and cardiovascular and cerebrovascular diseases (Altan, 2003). The global prevalence of diabetes mellitus is projected to reach 4.4% by 2030, with high occurrence reported in India, China, and the United States. In Kashmir Valley, the prevalence has shown a rising trend due to increasing stress and lifestyle changes (Alberti, 1982). A cross-sectional population survey conducted in 2006 reported a prevalence of known diabetes of 1.9% among adults aged over 40 years (Rahman *et al.*, 1990; Modak *et al.*, 2007). Diabetes mellitus is also associated with significant economic burden. Medicinal plants have been used since antiquity across civilizations as sources of therapeutic agents (Jarald *et al.*, 2008).

Mangifera indica L., belonging to the family Anacardiaceae, is one of the most economically important tropical fruit crops worldwide and is traditionally valued for its medicinal properties (Barreto *et al.*, 2008). Mango

trees are native to South and Southeast Asia. In 2018, global mango production, including guavas and mangosteens, was estimated at 55.4 million tonnes, with major producing countries including India, China, Thailand, Indonesia, Pakistan, Mexico, Brazil, Bangladesh, Nigeria, and the Philippines. Beyond the fruit, mango trees generate substantial agricultural residues such as leaves, flowers, stems, and bark. Mango leaves contain minerals such as nitrogen, potassium, phosphorus, iron, sodium, calcium, magnesium, and vitamins A, B, C, and E, as well as proteins, making them useful for various applications.

Metformin, a biguanide oral antidiabetic agent, is the first-line treatment for type 2 diabetes mellitus, particularly in overweight or obese patients with normal renal function (Begum *et al.*, 2017). Concomitant use of herbal medicines with conventional drugs has been reported to result in interactions, toxicities, or adverse effects (Saidulu *et al.*, 2014). These interactions may be antagonistic or synergistic and may influence drug absorption, distribution, metabolism, and elimination (Chavez *et al.*, 2006).

Drug interaction occurs when the effect of a drug is altered by the presence of another substance, including herbal medicines, foods, beverages, or environmental chemicals. Given the paucity of data on the effect of *Mangifera indica* seed on the dissolution behaviour of metformin tablets, this study was designed to evaluate the *in vitro* dissolution profile of metformin in the presence of *Mangifera indica* seed ethanolic

extract. Understanding such interactions is essential for healthcare professionals to ensure safe and effective drug therapy.



Figure 1: Authenticated Mango Tree (*Mangifera indica*).



Figure 2: Authenticated seeds of Mango (*Mangifera indica*).

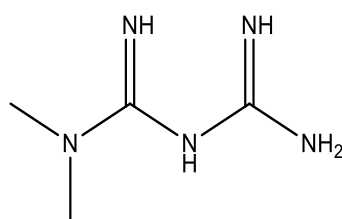


Figure 3: Molecular structure of Metformin Hydrochloride

Materials and Methods

Materials

Beakers (50 mL, 100 mL, and 800 mL; Pyrex, England); conical flasks (50 mL and 100 mL; Pyrex, England); measuring cylinders (10 mL, 100 mL, and 1000 mL; Pyrex, England); volumetric flasks (25 mL, 50 mL, and 100 mL; Pyrex, England); Whatman filter paper (Swastik Scientific Company, UK); mortar and pestle; spatula; foil paper; quartz cuvette; stopwatch; and test tube rack were used in the study.

The analytical instruments included an analytical balance (AR223CN, OHAUS Corporation, Pine Brook, NJ, USA), pH meter (HI9313-5, Hanna Instruments, USA), rotary shaker (M/C SR No. RS 693, Ambala Cantt, Haryana, India), oven (Model DEG-9330, Yamato Scientific Co. Ltd., Japan), digital friability test apparatus (Model 902), USP disintegration test apparatus (Model

1901), dissolution test apparatus (Hindustan Apparatus Management Company, India), UV-visible spectrophotometer (UV752, PEC Medical, USA), and a Monsanto hardness tester.

The reagents and solvents used were distilled water, potassium dihydrogen orthophosphate solution (0.68% w/v), 0.1 N sodium hydroxide, and methanol (Loba Chemi Pvt. Ltd., India).

Sampling of Metformin Hydrochloride Tablets

Five brands of metformin hydrochloride tablets (500 mg) were randomly purchased from pharmacies located in Kawo and Sabon Tasha areas of Kaduna metropolis, Kaduna State. Details of the brands, batch numbers, NAFDAC registration numbers, manufacturing dates, and expiry dates are presented in Table 1.

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

Brand	Brand A	Brand B	Brand C	Brand D	Brand E
Batch No.	CC07714	231008	2308069	FPC080524	230513
Nafdac No.	04-0810	B4-9596	C4-0303	04-6426	A4-2031
Production Date	07/2023	10/2023	08/2023	03/2024	05/2023
Expiration Date	06/2026	09/2026	07/2026	02/2027	05/2026

Collection and Identification of

Plant Material

Mangifera indica seeds were collected from Ungwan Rimi, Kaduna State, during the rainy season on 25 May

2025. The plant material was identified and authenticated by a taxonomist, Mallam U. S. Gallah. A voucher specimen (KASU/BSH/1213) was deposited in the Herbarium of the

Department of Pharmacognosy and Drug Development, Faculty of Pharmaceutical Sciences, Kaduna State University.

Preparation of Plant Extract

The seeds were cleaned, dehusked, chopped, and air-dried at room temperature for 18 days. The dried material was pulverised into a fine powder. A quantity of 134.6 g of the powder was extracted by cold maceration in 1 L of ethanol for 72 h (USP/NF XXIV). The extract was filtered and evaporated to dryness, yielding a percentage yield of 6.54%, indicating complete removal of ethanol.

Identification of Metformin

Hydrochloride by FTIR

Tablet samples and reference standards were powdered and analysed using

FTIR spectroscopy according to BP specifications to confirm identity.

Physicochemical Evaluation of Tablets

The tablets were evaluated for weight variation, hardness, friability, disintegration time, drug content, and dissolution using standard pharmacopeial procedures (USP/NF XXIV).

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;

$$\% \text{ Standard deviation} = \frac{\text{Individual Weight of tablets} - \text{average weight of tablets}}{\text{average weight of tablets}} \times 100$$

Hardness test

Ten (10) sampled tablets of each brand were selected. Each of the tablets was placed between the spindle of the Erwerka hardness tester machine and pressure was applied by turning the knurled knot just sufficiently to hold the tablet in position. The pressure was then applied as uniformly as possible until the tablet broke and the pressure required to break the tablet was recorded.

average

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 allowed for 4 minutes to oscillate at a drum speed of 25 revolutions per minute, the tablets were then removed, dusted and reweighed. Friability was determined using the formula:

$$\text{Friability} = \frac{W_1 - W_2}{W_2} \times 100$$

where: W_1 = initial weight and W_2 = final weight
Disintegration Time

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 $37 \pm 0.5^\circ\text{C}$ 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.

Drug contents

Randomly selection of 20 tablets was crushed into powder, a quantity of metformin powder equivalent to 500 mg was dissolved in 50 mL of 0.1 N HCl solution in a 100 mL volumetric flask and was made up to 100 mL with more 0.1 N HCl solution. Thereafter, it was filtered through Whatman filter paper. About 1.0 ml of this solution was transferred to 100 ml volumetric flasks, dissolved and volume was adjusted to mark. Absorbance of the resulting solution was measured at the maximum at 233 nm using UV-visible spectrophotometer. A plot of absorbance vs metformin concentration was drawn. The method used for assay of metformin tablet was adopted from the method reported by Ganesh *et al.*, (2018).

Dissolution Studies

Dissolution testing of metformin hydrochloride tablets alone and in the presence of *Mangifera indica* seed ethanolic extract was conducted using the BP paddle method at $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at specified

time intervals and analysed spectrophotometrically at 232 nm.

Dissolution test of metformin hydrochloride tablets alone

The dissolution of metformin was done according to the BP 2009, using the dissolution apparatus type II (paddle apparatus) at the rate of 100 rpm at $37 \pm 0.5^\circ\text{C}$ on six tablets of each brand, using 900 ml of a 0.68% w/v solution of potassium dihydrogen orthophosphate adjusted to pH 6.8 by the addition of 0.2M sodium hydroxide as the dissolution medium and rotating the basket at 100 revolutions per minute. About 10mls of the sample was withdrawn at 5,10,20,30,45, 60minutes and filtered. An equivalent volume of 10mls was replaced as fresh fluid in order to maintain sink condition. Absorbance of a layer of suitable thickness of the filtered sample was measured, using 'UV-visible spectrophotometer (UV752)' at the maximum at 232 nm.

Dissolution Study of metformin hydrochloride in the Presence of mangifera indica

After heating the dissolving medium to $37 \pm 0.5^\circ\text{C}$, 1 g of *mangifera indica* extract was added to the dissolution vessels, which contained a 0.68% w/v potassium dihydrogen orthophosphate solution. The mixture was then agitated with 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.

Data Analysis

Data were analysed using Microsoft Excel 2007, Origin graphing software, and SPSS version 22. Statistical significance was assessed using one-way ANOVA at a 95% confidence interval ($P < 0.05$).

Results and Discussion

From the results of fourier transform infrared (FTIR) spectra of brand A-E figures 4-8, 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, 2009).

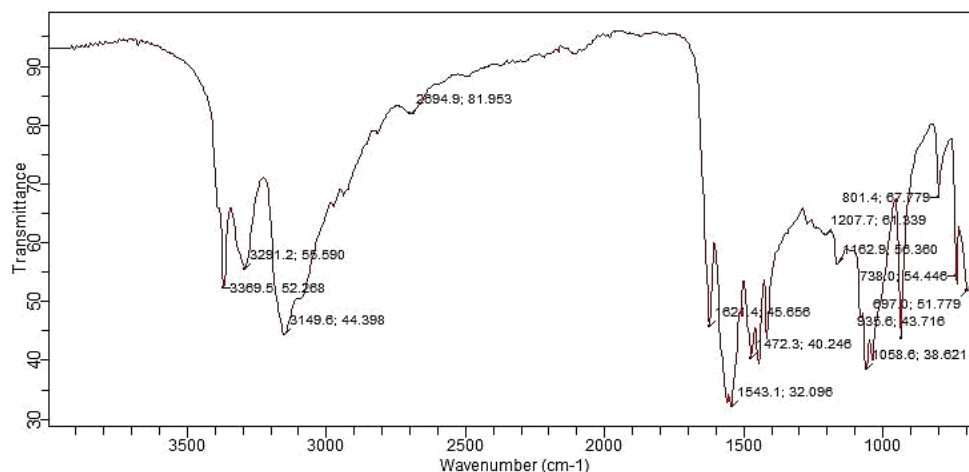


Figure 4: Fourier transform infrared (FTIR) spectra of Brand A

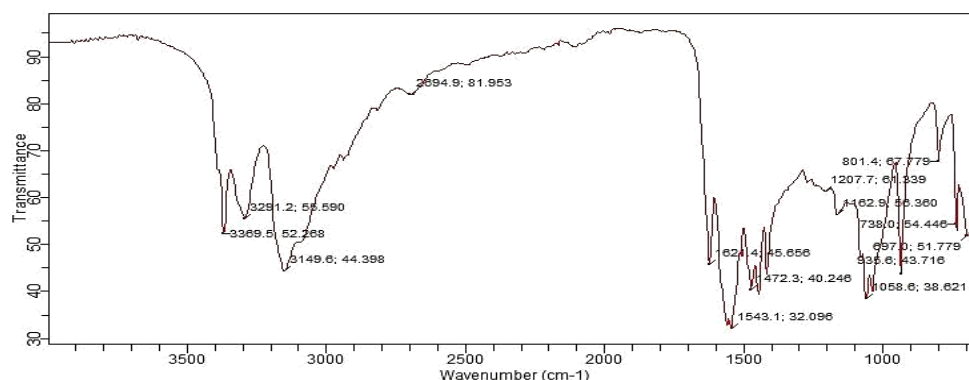


Figure 5: Fourier transform infrared (FTIR) spectra of Brand B

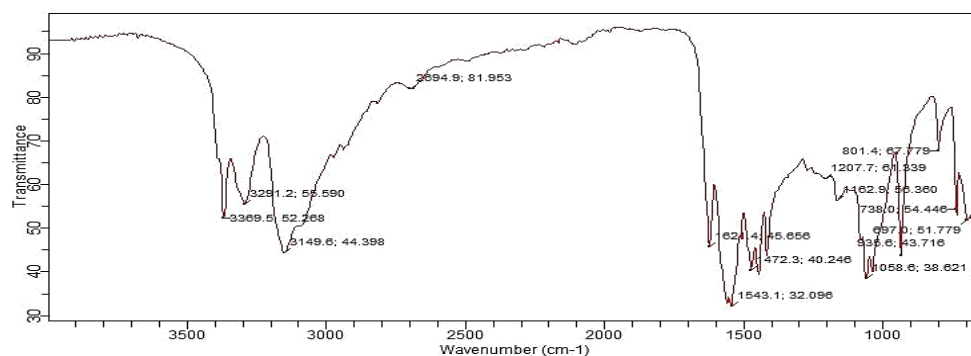


Figure 6: Fourier transform infrared (FTIR) spectra of Brand C

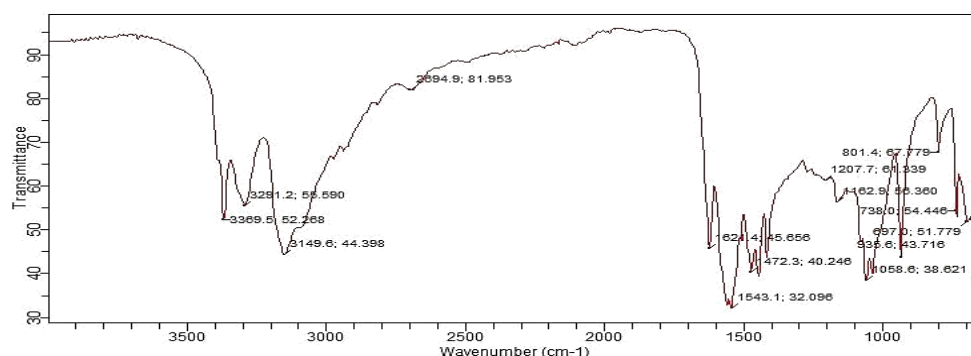


Figure 7: Fourier transform infrared (FTIR) spectra of Brand D

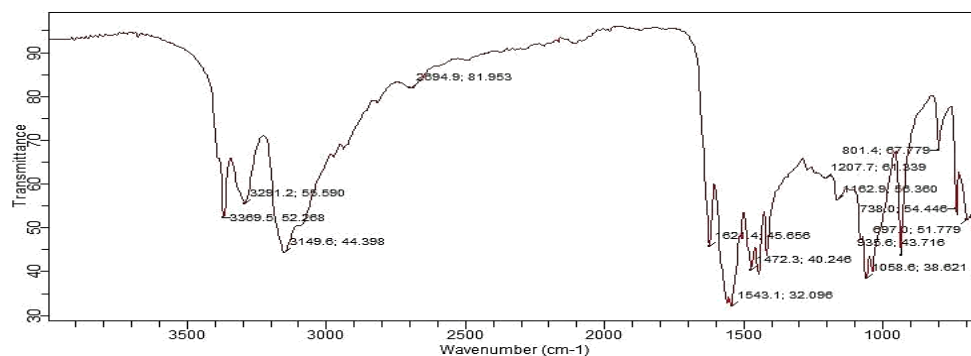


Figure 8: Fourier transform infrared (FTIR) spectra of Brand E

According to official pharmacopeial standards, tablet hardness and strength are critical parameters in ensuring that tablets weighing more than 324 mg comply with the permitted weight variation limit of $\pm 5\%$ and are able to withstand shock and stress during manufacturing, packaging, transportation, and patient handling. It was found that all the tablets complied with the USP specifications for weight

variation, as none of the brands deviated beyond the acceptable limits. Based on the findings, all brands deviated by not more than $\pm 5\%$ from the mean tablet weight and therefore passed the weight variation test (USP, 2007).

This indicates that the factors influencing weight variation were adequately controlled during tablet production (Odeniyi *et al.*, 2003). The

minimum diametric crushing force required for a satisfactory tablet is 4 kg/f, which reflects the tablet's ability to withstand fracture. Weight variation provides a rough estimate of content uniformity; although it is not a confirmatory test, the metformin hydrochloride tablet brands evaluated

showed acceptable uniformity. The weight uniformity test also reflects tablet strength, as all brands exceeded the minimum crushing force of 4 kg/f, ensuring that the drug content in each unit dose is distributed within a narrow range around the label claim (**Table 2**) (Akwas *et al.*, 2016; USP, 2007).

Table:2 Physicochemical parameters of the different brands of Metformin hydrochloride tablet

Parameters	Brand A	Brand B	Brand C	Brand D	Brand E
Weight variation (g)±SD	-0.18±0.50	0.57±0.49	-0.74±0.35	0.49±0.68	0.74±0.69
Hardness (Kg/F) ±SD	6.19±0.43	7.29±0.33	6.70±0.33	5.85±0.29	6.67±0.43
Friability (%)	0.08±0.03	0.38±0.07	0.33±0.09	0.47±0.19	0.37 ±0.17
Disintegration time ± SD (Min)	6.53±0.43	4.53±0.12	7.10±0.32	7.11±0.24	7.48±0.33
% Purity	92.07	95.21	97.23	91.83	97.02

Thus, this implies that all of the tablets can withstand the real-world stress and rigorous transportation processes that the drug must undergo before consumption. If a tablet breaks, chips, or turns into powder, the patient may not receive the proper dose of the drug, which could be lower than the recommended dose (Hailu *et al.*, 2011). When compressed and uncoated tablets are subjected to mechanical shock and attrition, friability is used as a measure of their physical strength. Friction and shock are the most common causes of tablet chipping, cracking, and breaking.

The friability test is related to tablet hardness and is used to assess a tablet's ability to tolerate abrasion during packaging, handling, and shipping. According to the British Pharmacopoeia and Indian Pharmacopoeia (B.P./I.P.), the

percentage friability should not exceed 0.8–1.0%, while according to the United States Pharmacopoeia (U.S.P.), the percentage friability should not be more than 4% (BP, 2009). The results of the friability test showed that all the brands tested had acceptable friability values ranging from 0.149% to 0.664%, as shown in **Table 2**.

Disintegration refers to the breakage of inter-particle interactions generated during tablet compaction of granulated particles of the active pharmaceutical ingredient (API) and excipients, and it is a physical process related to the mechanical breakdown of a tablet into small particles or granules. The disintegration time of uncoated and coated tablets should not exceed 15 and 30 minutes, respectively (BP, 2009). The observed disintegration times for all brands of metformin hydrochloride

tablets examined were shorter than the official compendial limit of 15 minutes (**Table 2**), indicating compliance with pharmacopeial requirements. The type and quantity of excipients used in tablet formulation, as well as the manufacturing process, are known to influence both disintegration and dissolution parameters (Muaz *et al.*, 2009).

Assay Test

The test for percentage content is based on the assay of the individual content of the active ingredient in a number of single-dose units. The average chemical content (assay) is determined from the assay of the active ingredient in these units. The average assay values obtained were within the monograph specifications of 95–105% for metformin tablets, as shown in **Table 2**. The results from the assessment of the percentage content of the active ingredient in one of the brands of metformin tablets showed that it passed the assay test with a value of 96.6% (BP, 2009).

Dissolution Test

This *in vitro* study demonstrated that the dissolution of metformin in the presence of *Mangifera indica* was reduced, possibly due to the limited absorption capacity of the drug when combined with *Mangifera indica*. Several factors may have contributed to the interaction between *Mangifera indica* and metformin. First, *Mangifera indica* contains flavonoids, alkaloids, and phenolic compounds, which may be responsible for the observed interaction, as shown in **Table 3**. Second, *Mangifera indica* also contains trace elements and minerals such as

calcium, aluminium, magnesium, potassium, sodium, zinc, and copper, some of which are known to cause drug interactions through chelate formation (Luca *et al.*, 2020).

Similarly, the presence of flavonoids, alkaloids, and phenolic compounds in *Mangifera indica* may further explain its interaction with metformin. In addition, the trace elements and minerals present in *Mangifera indica*, including calcium, aluminium, magnesium, potassium, sodium, zinc, and copper, are known to contribute to herb–drug interactions through chelate formation (Luca *et al.*, 2020).

According to BP (2009), more than 75% of the stated amount of metformin hydrochloride should be released within 45 minutes for solid oral dosage forms. From the dissolution test results shown in **Figure 9**, all brands of metformin hydrochloride tablets released more than 75% of the drug within 45 minutes, indicating that the dissolution profiles of all the brands met the BP (2009) criteria when tested alone. Dissolution of drugs can be influenced by the physicochemical properties of the drug substance, dosage form design, manufacturing process, and testing conditions such as the apparatus, agitation speed, and dissolution medium.

Dissolution and bioavailability of drugs can also be influenced by formulation components and drug manufacturing procedures. Tablets produced by dry granulation, wet granulation, or direct compression may behave differently under *in vitro* and *in vivo* conditions respectively. These factors directly

influence the breakdown of dosage forms in gastrointestinal fluids and subsequently affect drug absorption

(Oussama and Mostafa, 2016, Garba *et al.*, 2021).

Table 3: Qualitative phytochemical profile of ethanolic seed extract of *Mangifera indica*

Phytochemical	Test	Inference
Carbohydrate	Molishs Test	+
Saponins	Frothings Test	+
Flavonoids	NaoH Test	+
Alkaloids	Dragendroffs Test	+
Cardiac Glycosides	Keller Kilians Test	+
Anthroquinones	Bontragers Test	+
Terpenoids	Salkowski Test	+

Key: + Present; - Absent

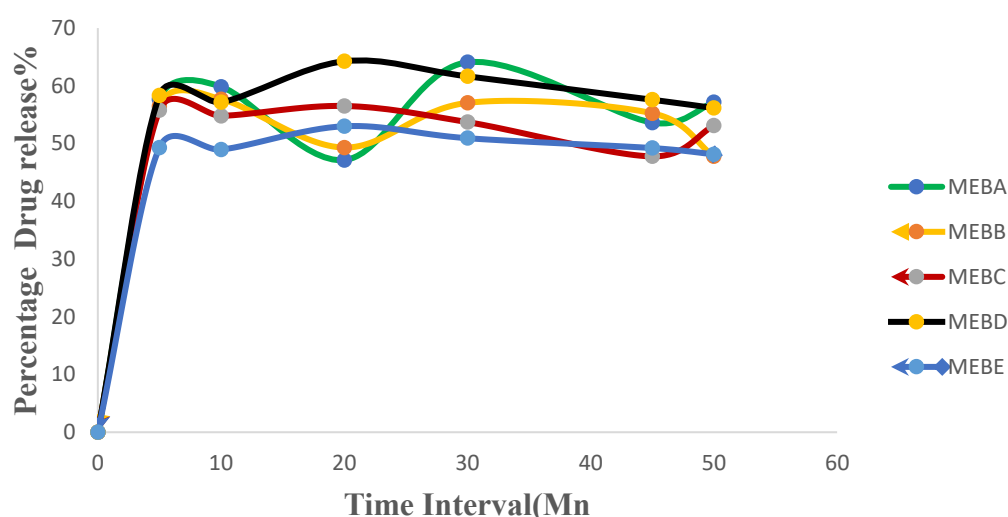


Figure 9: Dissolution Profile for the Different Brands of the Metformin Tablets alone and in the presence of Mango extract

Key:MEBA - Mango Extract + Brand A; MEBB - Mango Extract + Brand B; MEBC - Mango Extract + Brand C; MEBD - Mango Extract + Brand D; MEBE - Mango Extract + Brand E;

Conclusion

This *in vitro* study demonstrates that *Mangifera indica* seed ethanolic extract significantly alters the dissolution profile of metformin hydrochloride tablets. Concomitant administration of *Mangifera indica* and metformin may

reduce the metformin bioavailability and potentially compromise therapeutic efficacy.

Conflict of Interest

The authors declare no conflicts of interest.

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