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SPECTROSCOPIC EVALUATION OF THE METHANOLIC EXTRACT OF *AZADIRACHTA INDICA* ON THE DISSOLUTION OF METFORMIN

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ABSTRACT

Background:-Herbal remedies continue to play a significant role in the healthcare of a huge portion of the developing world's population, particularly those living in rural regions. This is because such communities are frequently underserved in terms of Western-style healthcare, resulting in a larger reliance on traditional medicine for disease management, which is both more accessible and more culturally acceptable. A drug interaction is said to occur when the effect of one drug is changed by the presence of another substance, which may be a drug, herbal medicine, food, drink, or an environmental chemical agent.

Aim: The study is aimed at determining the effect of Azadirachta indica on the metformin dissolution profile.

Methods: Five samples were taken at regular intervals during the dissolving process from a potassium dihydrogen orthophosphate medium that had been pH-adjusted to 6.8 using 0.1M NaOH. The process of dissolution was used to replicate the pH of the gastrointestinal system both with and without the herbal medication.

Results: The results showed that when metformin was added to the dissolving medium alone as opposed to when it was combined with Azadirachta indica, a larger percentage of the medicine was released.

Conclusion: As a result of the study's finding Azadirachta indica increases the percentage release of metformin tablets. co-administration of Azadirachta indica with metformin should be avoided. The dissolution profile of metformin was enhanced in the presence of azadirachta indica. This may result in therapeutic failure.

Keywords: Azadiracta indic; dissolution profile; herbal medicine; metformin.

1.0 INTRODUCTION

Azadirachta indica, a member of the Meliaceae family, has a long history of use as a remedy for many illnesses [1,2]. The plant is referred to as "Dogonyaro" in Nigeria [3,4]. According to ancient medical research, neem leaf extracts are used to treat malaria, skin infections, skin ulcers, diarrheal, and intestinal diseases [2]. Alkaloids, tannins, flavonoids, and phenolic compounds are some of the phytochemical compositions in neem that are the most significant bioactive

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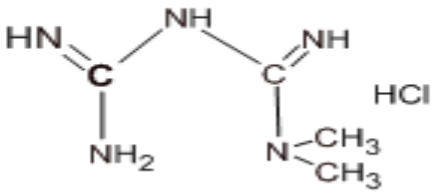
components of plants [5]. Formamidinyl urea is a source of biguanides. It is the first-line therapy and management option for all types of diabetes, particularly Type 2 diabetes. Their workings are complicated and still not fully understood. They lessen hepatic glucose production, improve skeletal muscle glucose uptake and utilization, and diminish insulin resistance (gluconeogenesis) [5]. The undesirable side effects of metformin are dose-related gastrointestinal disturbances, which are typically but not always temporary and include anorexia, diarrhea[5], and nausea. Patients with type 2 diabetes typically utilize metformin in clinical settings. Since it does not increase hunger, it is helpful for the vast majority of type 2 patients who are obese and who do not respond to diet-only therapy. It can be used with sulfonylureas, glitazones, or insulin and does not result in hypoglycemia [6]. A drug interaction is said to occur when the effect of one drug is changed by the presence of another substance, which may be a drug, herbal medicine, food, drink, or an environmental chemical agent. Good knowledge of the potential of commonly consumed herbal medicines interacting with prescription medicines will equip health professionals in their practice. Apart from those demonstrated in a significant number of human subjects, not all reported herb-drug interactions (HDIs) are clinically significant. As such, more clinically relevant research in this area becomes necessary [6,7].

Figure 1:- Authenticated leaves of *Azadirachta indica*



***N,N*-dimethyltrimidodicarbonicdiamide-hydrogen chloride (1/1)**

Figure 2: Molecular structure of metformin hydrochloride

2.0 MATERIALS AND METHODS

2.1 Materials

Beaker (800ml, 100ml, 50ml Pyrex, England), Conical flask (100ml, 50ml Pyrex, England), Measuring cylinder (1000ml, 100ml, 10ml Pyrex, England), Volumetric flask (100 ml, 50ml, 25ml Pyrex, England), Whatman filter paper (Swastik Scientific Company, UK), 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), Digital friability test apparatus (Model 902), U^{p} disintegration test apparatus (Model 1901), Dissolution test

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apparatus (Hindustan Apparatus Management Company, India), UV-visible spectrophotometer (UV752, pec medical USA), Monsanto hardness tester, Oven, Friability device

2.2 Solutions and Reagents

Distilled water, Solution of potassium dihydrogen orthophosphate (0.68% w/v), 0.1N Sodium hydroxide, Methanol (Loba Chemi Pvt. Ltd., India), 0.1N HCl.

2.3 METHODS

2.3.1 Sampling of Metformin Tablet

The type and brand of metformin (500 mg) used in the study were obtained randomly from Pharmacy stores within Kaduna metropolis and Unguwan Rimi, Kaduna State (Table 1).

2.3.2 Collection and Identification of Plant Material (*Azadirachta indica*)

The leaves of ***Azadirachta indica*** were collected in KASU environs early in the morning on the 24th of November, 2021. The leaves were identified by a taxonomist Mallam U.S. Gallah and were authenticated at the herbarium of the Biology Department Kaduna State University, batch number KASU/PCG/060 Kaduna state.

2.3.3 Herbal Preparation and Extraction

Drying and Size Reduction

Azadirachta indica leaves were cleaned and subsequently, air dried for seven 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 [7].

2.3.4 Extraction

The fine powder (121.4 g) of *Azadirachta indica* was extracted using the cold maceration method for 24 hours with 200 ml of 70% methanol [6,7]. The extract was filtered and allowed to evaporate to dryness in a water bath, yielding a constant yield and a percentage yield of 9.3%, indicating that the methanol has been completely removed from the extract [6,4,8].

$$\text{Percentage weight loss} = \frac{weight\ of\ extract}{powder\ sample}\ x\ 100$$

2.4.0 Preliminary Qualitative Phytochemical Screening

Phytochemical screening for the presence of saponins, tannins, phenolics, flavonoids, alkaloids, cardiac glycosides, carbohydrates and steroids/ triterpenes was conducted using the method described [8]. The hydroethanolic leaf and root extracts were subjected to phytochemical screening to identify their phytochemical constituents.

2.4.1 Test for Alkaloids

2.4.1.1 Mayer's Test: A small portion of the leaf extract was dissolved in 2 ml of distilled water. The solution was shaken and filtered. To the filtrate, a few drops of Mayer's reagent were added. The formation of a cream-colored precipitate would indicate the presence of an alkaloid [9]. The procedure above was repeated for the root extract.

2.4.2 Test for Saponins

2.4.2.1 Frothing Test: A small portion of the leaf extract was dissolved in 10 ml of water and shaken vigorously for 30 seconds and allowed to stand for one hour. The reactant was observed for the occurrence of a frothing column or honeycomb-like of at least 1 cm in height and persisting for at least 30 minutes [9].

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2.4.3 Test for Steroids/Terpenes

2.4.3.1 A Leiberman-Burchard test: To a small portion of the *A.indica* leaf extract in a test tube, an equal volume of acetic acid anhydride was added and mixed gently. One millilitre of concentrated sulphuric acid was added down the test tube wall. The reactant was observed for the development of Blue to blue-green colouration in the upper layer and a reddish, pink or purple colouration at the junction of the two layers [4, 9]. The procedure above was repeated for the root extract.

2.4.3.2 B. Salkowski test: Small portion of the *A. indica* leaf extract was dissolved in 2 ml of chloroform, and 3 drops of concentrated sulphuric acid were added at the side of the test tube. The tube content was observed for the formation of a reddish-brown coloration at the interface [9]. The procedure above was repeated for *A. indica* leaf extract.

2.4.4 Test for flavonoids

2.4.4.1 Ferric Chloride Test: 2 drops of ferric chloride solution were added to a solution of *A.indica* leaf extract in distilled water. The observation was made for the development of green coloration. The procedure above was repeated for *A.indica* leaf extract.

2.4.5 Test for cardiac glycosides

2.4.5.1 Keller-Kiliani test: A small portion of the leaf extract of *A.indica* leaf was dissolved in 1 ml of glacial acetic acid containing traces of ferric chloride solution. An equal volume of sulphuric acid was added to the tube content and observed for the formation of a brown ring at the interface [9]. The procedure above was repeated for *A. indica* leaf extract.

2.4.6 Test for carbohydrate

2.4.6.1 Fehling's test: To a small portion of the extract in a test tube, 5 ml of an equal mixture of Fehling solution A and B was added and boiled in a water bath and observed for the formation of a brick red precipitate [9].

2.4.7 Test for anthraquinones

2.4.7.1 Bontrager's test: A portion of the extract was dissolved in 5 ml chloroform. The solution was then shaken and filtered. To the filtrate, an equal volume of 10% ammonia solution was added and was shaken continuously and observed for the formation of bright pink colour in the aqueous upper layer [9].

2.5.0 Preliminary Physicochemical Evaluation of Tablets

Metformin tablets containing 500 mg of metformin hydrochloride were subjected to some preliminary physicochemical evaluations such as physical identification, weight uniformity, friability, and crushing strength using standard procedures. A drug quality assessment experiment was done using pharmacopeial procedures described in the USP/NF XXIV, USP [10].

2.5.1. Identification

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 FTIR equipment for analysis.

2.5.2 Weight variation

Twenty (20) metformin tablets of each brand were weighed individually using an analytical weighing balance and their arithmetic mean weighed and relative

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standard deviation were determined. The result was calculated using the formula below:-

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

Where: W1 = initial weight and W2 = final weight

2.5.3 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 ^{0}C was 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.

2.5.4 Drug Content Assay

Randomly selection of 20 tablets was crushed into powder, and 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 the Whatman filter paper. About 1.0 ml of this solution was transferred to a 100 ml volumetric flask, dissolved and the volume was adjusted to mark. The absorbance of the resulting solution was measured at a maximum of 233 nm using UV- a visible spectrophotometer. A plot of absorbance vs metformin concentration was drawn. The method used for the assay of metformin tablets was adapted from the method [11].

2.5.5 Friability Test

From the various brands of metformin, 10 tablets were brushed to remove the surface powder and then weighed accurately, the tablets were then placed in a "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:-

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

2.6 Invitro dissolution study of metformin tablets alone

The dissolution of the metformin tablet was done according to the [12] specification using dissolution apparatus type II (paddle apparatus) at a rate of 100 rpm at 37±0.5∘C using one tablet of each brand. Ten milliliters (10 ml) of samples were withdrawn at 5, 10, 20, 30, 45, and 60 min and an equivalent amount of fresh dissolution medium was used to replace them. Filtered samples were then appropriately diluted and absorbance readings were taken with UV/Visible Spectrophotometer at a wavelength of 232 nm. The concentration of each sample was determined.

2.7 Invitro dissolution study of Metformin tablet in the presence of *Azadirachta indica*

The dissolution medium was heated to 37 ± 0.5 ^{0}C, and 1 g of *A. indica* extract was added to dissolution vessels (containing 500 ml of distilled water) to form a solution and stirred with a glass rod. One tablet of metformin was placed in the vessel and the dissolution vessel was immediately

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operated at 50 rpm for 15 minutes. Five sampling points (5, 20, 30, 45, and 60 minutes) were defined to monitor the dissolution. At each sampling point, a 5 ml sample was collected using a syringe between the surface of the dissolution medium and the top of the rotating paddle. The mixture temperature was periodically verified and the vessel was kept covered over the entire duration of the dissolution test. The samples were filtered with a membrane filter before analysis by UV spectrophotometry at 233 nm and the absorbance of each sample was taken.

2.8 Data Analysis

Data obtained were treated using the ORIGIN graphing and scientific analysis software program and Microsoft Excel 2007.

3.0 RESULTS

The result of Fourier transform infrared spectra (FTIR) of brands A-E are shown in Figure 3 to Figure 7, also the Physicochemical parameters of all the brands of metformin tablets (A-E), and qualitative Phytochemical analysis are indicated in Tables 2 and 3 respectively**.** The Comparative dissolution profile of different brands of metformin alone and when combined with Azadirachta *indica(herbs) are shown in* Figure 3-7.

Table 1: The description of the metformin tablets used in the study

	Product A	Product B	Product C	Product D	Product E
Batch number	2121	A202083	210106	CA09686	07654
NAFDAC number	A4-6597	04-7945	A4-6354	04-0810	A4-0976
Production date	05/2021	10/2020	01/2022	09/2020	05/2021
Expiry date	05/2024	09/2023	01/2025	08/2023	10/2024

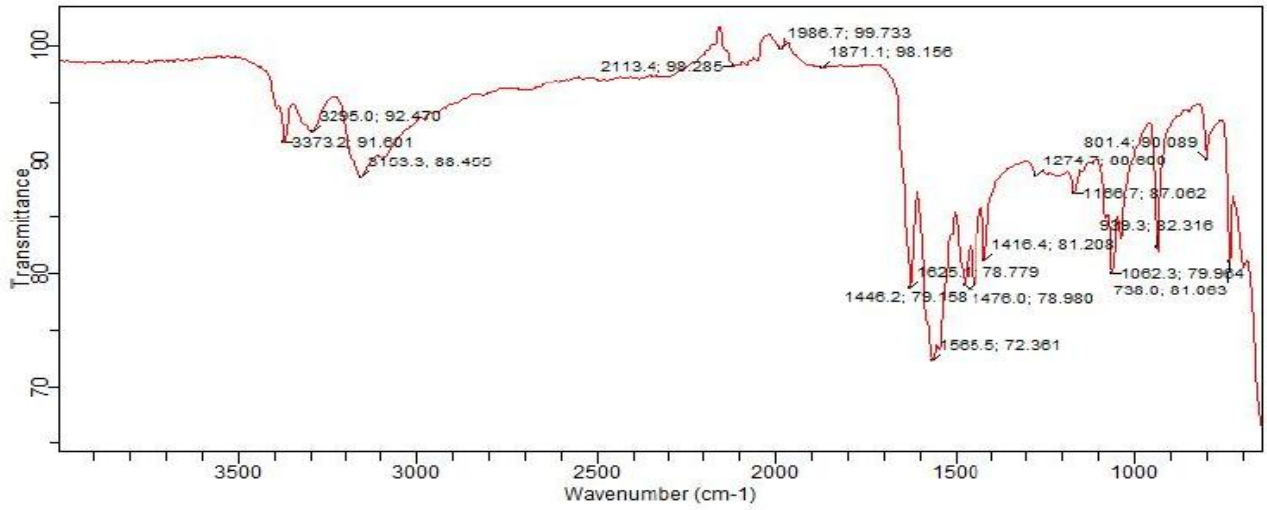

Figure 3: Fourier transform infrared (FTIR) spectra of brand A

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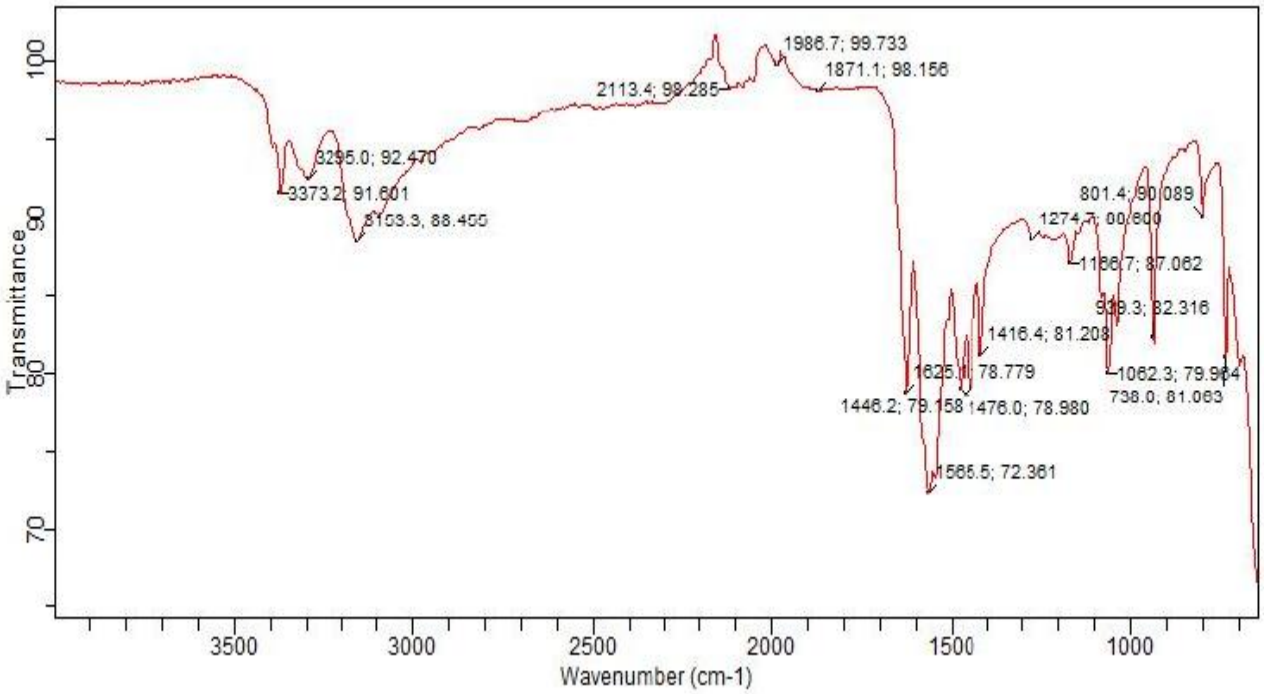

Figure 4: Fourier transform infrared (FTIR) spectra of brand B Metformin

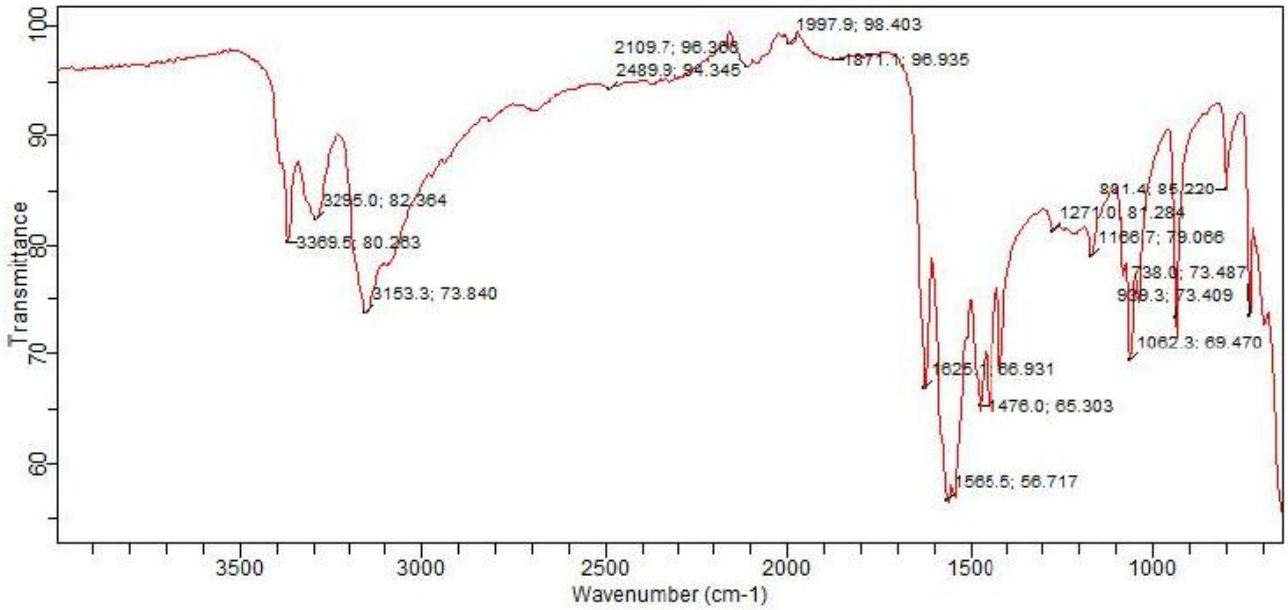

Figure 5: Fourier transform infrared (FTIR) spectra of brand C of metformin

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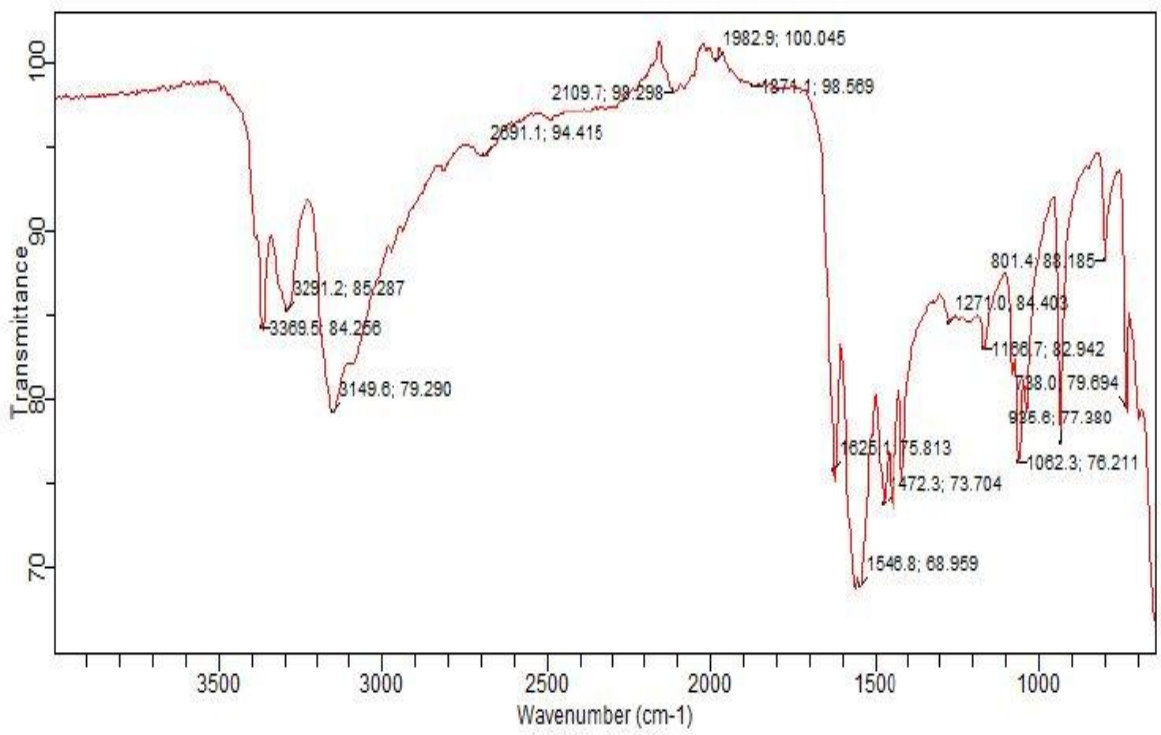

Figure 6: Fourier transform infrared (FTIR) spectra of brand D

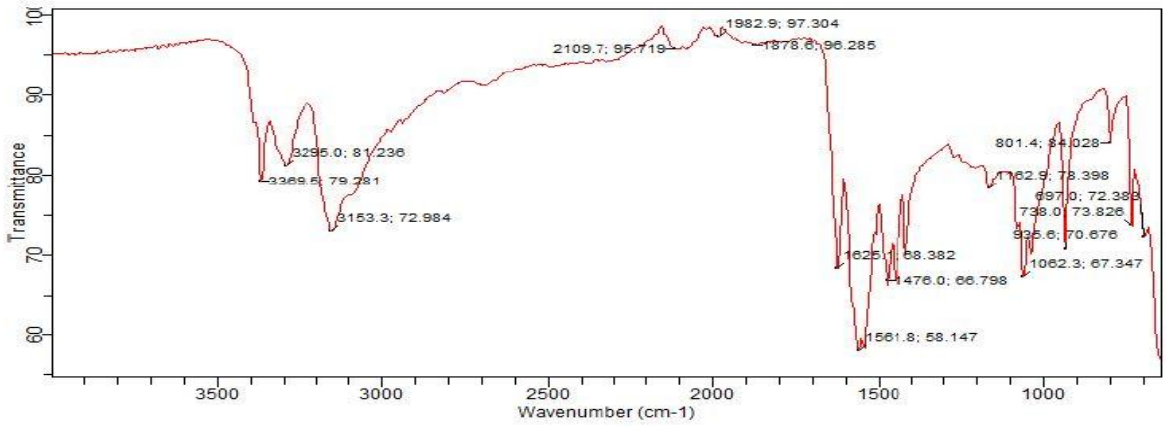

Figure 7: Fourier transform infrared FTIR) spectra of **brand E**

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Table 2: Physicochemical Parameters of the Different Brands of Metformin Hydrochloride Tablets

Brand	Uniformity of Weight (g) ± SD	Hardness(kg/f)	%Friability	% Purity	Disintegration Time (min)
A	0.533±0.005	8.63±1.28	0.165	99.06	7 min 52 sec
B	0.564 ±0.008	7.23±1.35	0.512	91.29	5 min 30 sec
C	0.618± 0.120	4.29±2.08	0.365	91.09	5 min 15 sec.
D	0.562± 0.120	5.07 ±1.26	0.563	92.04	7 min 30sec
E	0.634±.0231	4.59±1.40	0.651	95.01	6 min 30 sec

Table 3: Qualitative Phytochemical Analysis of the Plant Extracts of *Azadirachta indica*

S/N	Test	Observations
1	Saponin	+
2	Alkaloid	-
3	Carbohydrates	+
4	Flavonoids	+
5	Cardiac glycosides	+
6	Steroids/Triterpenoids	+
7	Anthraquinones	-

Keys: (+) = **Presence** (-) = **Absence**

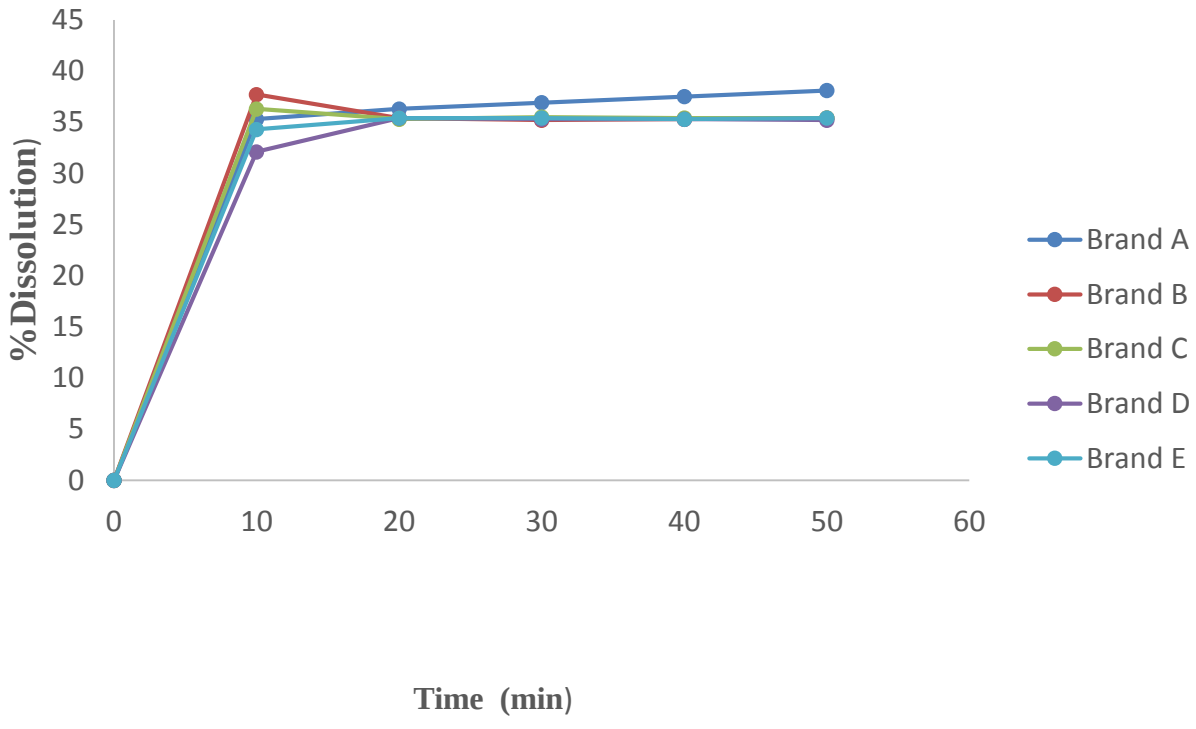

Figure 8: Graphical Presentation of Average % Drug Releases of Metformin Tablets of Brand A – E

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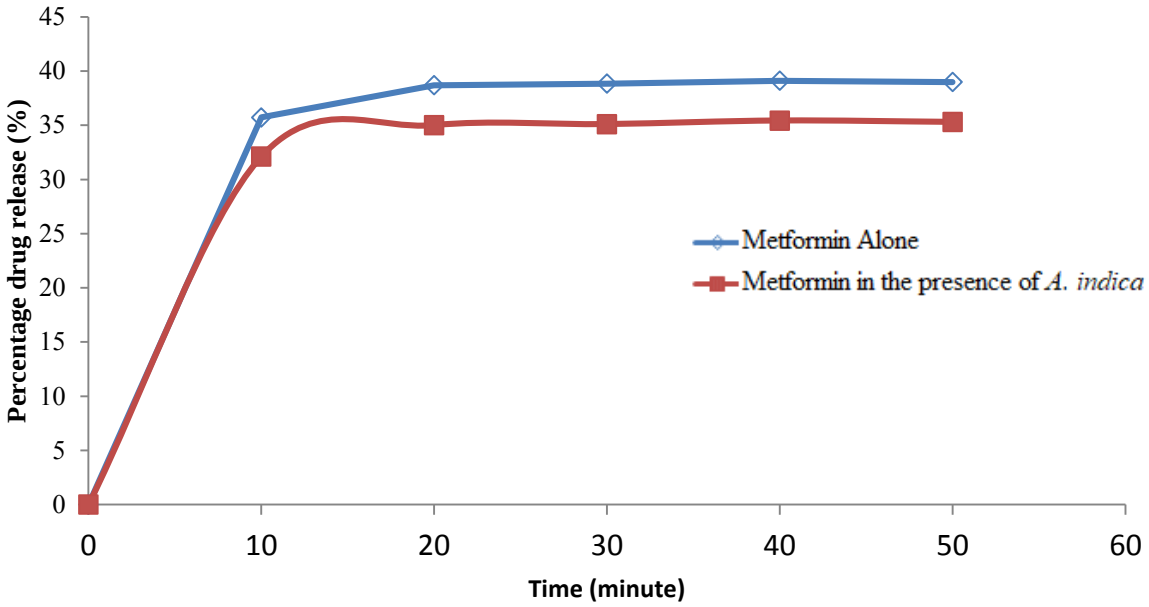

Figure 9: Graphical Presentation of Average % Drug Releases of Metformin Tablet in the presence of *Azadirachta indica*

4.0: DISCUSSION

From the results of Fourier transform infrared spectra (FTIR) of brands A-E it was confirmed that all of the brands were identified to be metformin. Stretching and deformation vibrations (4000–1400 cm^{-1}) and a near fingerprint cause the functional groups' absorption bands (1400 – 900 cm^{-1}). All the Brands were found to be superimposable and relatively similar to the reference standard [10].

Over time, research has shown that *Azadirachta indica* is rich in a wide range of compounds, of which several have pharmacological potential. Out of all these compounds, saponins, triterpenes, and flavonoids were found in *Azadirachta indica* leave extract [2]. In this study, the methanol extract of *Azadirachta indica* shows the presence of Saponin, carbohydrate, cardiac, and glycoside, but alkaloids and anthraquinones are not present.

Also, the weight variation provides a general indication of content uniformity. To make sure that the drug content in each unit dose is distributed in a constrained range around the label strength, a weight uniformity test is necessary [10]. According to official books, the specified limit weight variation for tablets containing more than 324 mg is 5%. The result of weight variation indicated that all metformin tablets had passed the test.

The hardness of the tablet is essential for ensuring that it can withstand shock and stress during production, packaging, and shipping, as well as when managing patients. Every tablet passed the weight variation test [13].

The minimum crushing force required to produce an acceptable tablet is 4 Kg/f diametric. As they all exceeded the necessary 4 kg/f, all brands of metformin hydrochloride tablets had the best ability to sustain breakage. Table 4 displays the brands A, B, C, D, and C thus Inferring that all of the tablets have passed the hardness test [14].

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Friability is a metric used to assess the physical toughness of compressed and uncoated tablets when they are put through mechanical shock and attrition. The most frequent reasons why tablets chip, chop, and break are friction and shock [10]. The friability test measures a tablet's resistance to abrasion during handling, shipping, and packing. It is linked to tablet hardness. The percentage of friability should range between 0.8% and 1.0%, according to B.P/I.P. The percentage of friability should not exceed 4%, according to [10]. Table 5 indicates that all have passed the test.

The value is expressed using the percentage. A maximum weight loss of 1% of the weight of the tablets being tested is considered acceptable during the friability test, and any broken or smashed tablets are not picked up. Typically, friability values are not determined when capping occurs [15]. The results of the tablet friability test were displayed in Table 5 and revealed that all brands examined (A–E) had fair friability values ranging from 0.61 to 0.98%. According to the findings, all brands can endure abrasion during handling, packaging, and shipment [12].

Disintegration is a physical process involving the mechanical disintegration of a tablet into minute particles or granules. Uncoated and coated tablet disintegration times shouldn't be longer than 15 and 30 minutes, respectively [12]. From the study, the disintegration time of all metformin brands was within the accepted range of 15 minutes. Brand D which was the quickest, disintegrated in 5.31 minutes, whereas brands A, B, C, and E took 7.29 minutes, 9.75 minutes, 7.81 minutes, and 7.16 minutes, respectively to disintegrate. The variance in disintegration time may have resulted from the usage of various disintegrants by various brands to encourage aqueous liquid penetration [16].

More than 75% of the specified amount of metformin hydrochloride should be released after oral administration within 45 minutes [12]. Based on the study, all five brands had a release rate of more than 75% in 45 minutes, which means they have satisfied the standards test.

The average chemical content (assay) of metformin tablets falls between the ranges specified in the monograph (95-105%). Brands of metformin tablets have passed the test of value with more than 94.5%, according to the results of the evaluation of the percentage content of active components in that brand [12].
Dissolution of Metformin in the presence of *A. indica*. Any interruption in the process of dissolution could affect the amount of the active drug in the systemic circulation, thereby altering the clinical effect of the drug [17, 18]. The in-vitro study has shown that in the presence of *Azadiracta indica*, there is an increase in the dissolution of metformin as a result of interaction between metformin and *Azadiracta indicia*, which may result in higher bioavailability of metformin.[18]

5.0 CONCLUSION

The different brands of metformin tablets used for the dissolution study were found to interact with the methanol extract of *Azadirachta indica* by causing an increase in the dissolution parameter of metformin. Also, phytochemical screening on the methanol extract of *Azadirachta indica* shows the presence of some important secondary metabolites. It is recommended that patients on metformin be advised to delay the consumption of the

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Conflicts of Interest

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

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