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EFFECT OF *ARTEMESIA ANNUA* ON *IN-VITRO* DISSOLUTION OF VARIOUS BRANDS OF METFORMIN TABLETS

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ABSTRACT

Background: Metformin is the world's most commonly used antidiabetic drug for type 2 diabetes and this is major because it protects against diabetes-related mortality. Concurrent administration of metformin with herbal medicines causes interaction, which may lead to undesirable pharmacokinetic and pharmacodynamic effects.
Aim: This study aimed to determine the effect of the methanol extract of *Artemisia annua* on the in-vitro dissolution of various brands of metformin tablets.
Method: Five brands of metformin (500 mg) tablets were randomly purchased from different Pharmacies within the Kaduna metropolis. The *in-vitro* dissolution of different metformin tablet brands with methanol extract of *Artemisia annua* was carried out according to the BP 2009, using the dissolution apparatus type II (paddle apparatus) at the rate of 100 rpm at 37 ± 0.5^0C, using the medium 900ml of a 0.68% w/v solution of potassium dihydrogen orthophosphate and the pH was adjusted to 6.8 by the addition of 1M sodium hydroxide while rotating the basket at 100 revolutions per minute.
Results: All the brands of metformin tablets complied with official specifications for hardness, friability, disintegration, and assay.
Conclusion: Therefore, based on invitro dissolution studies, the brands might be substituted with the innovator product in clinical practice. The results revealed that *Artemisia annua* lowers metformin's dissolution profile and subsequently its bioavailability.
Keywords: Metformin, *Artemisia annua*, *In-vitro*, Dissolution, Interaction

INTRODUCTION

Diabetes mellitus (DM) is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either a lack of insulin secretion or decreased sensitivity of the tissues to insulin [1]. Metformin is the most commonly prescribed oral antidiabetic drug in the world [2], and it works primarily by reducing hepatic glucose production through a complex mechanism of action [3]. Concurrent use of herbal and orthodox medicines causes interaction between these two forms of medicine which can lead to undesirable pharmacokinetics and pharmacodynamics as result of undesirable reactions that occur [4,5]. *Artemisia annua* L. is an herbal medicinal plant used in many cultures for treating many disorders including malaria [6,7]. Researchers reported that patients with diabetes who are placed on metformin therapy do combine with other herbal medicinal plants, especially *Artemisia annua* for treating disease condition such as malaria. However, the concomitant use of

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metformin and *Artemisia annua* may lead to desirable or undesirable pharmacokinetics and pharmacodynamics as a result of reactions that may occur. The present study aimed to determine the effect of the methanol extract of *Artemisia annua* on the in-vitro dissolution of various brands of metformin tablets.

MATERIALS AND METHOD

Glasswares: Different sizes of Beakers (Pyrex, England), conical flasks (Pyrex, England), measuring cylinders (Pyrex, England), test tubes, volumetric flasks (Pyrex, England), Whatman filter paper, Spatula, mortar and pestle, and stopwatch were used.

Equipment: Analytical balance, Rotary shaker, Friability test apparatus (Model 902), U^P disintegration test apparatus (Model 1901), Dissolution test apparatus (Hindustan Apparatus Management Company, India), UV-visible spectrophotometer (UV752, pec medical USA) and Monsanto hardness tester (model N1863).

Solutions and Reagents:
Distilled water, 0.1N HCl, methanol, and a solution of potassium dihydrogen orthophosphate (0.68% w/v)

Sampling of Metformin Tablet
Five brands of metformin (500 mg) were randomly purchased from different Pharmacies within the Kaduna metropolis.

Identification of metformin tablets by FTIR
The various metformin tablets were identified by the BP-specified method of the FTIR method. This was carried out by powdering the tablets, an equivalent of 200 mg was transferred into a conical flask and then dissolved in 20 mL of absolute ethanol and shaken. The admixture was then filtered and evaporated to dryness on a water bath, and the residue was then dried in an oven for an hour at 105ºC. The residue was then used; its spectra were recorded and compared with that of the monograph reference standard.

Collection, Identification, and Processing of the Plant Material (*Artemisia annua*)
Artemisia annua was purchased from an herbalist at Kaduna Central Market. The plant was identified by the taxonomist Mallam U.S. Gallah at the herbarium of the Biology Department, at Kaduna State University. The size of the plant was reduced into a fine powder with a mortar and pestle and stored in an air tight rubber container.

Extraction of *Artemisia annua*
The *Artemesia annual* extract was obtained by cold maceration process where 200g of the powder was soaked in 70% methanol in a 250 mL Eden Meyer flask for 72 hours at room temperature with intermittent shaking. The flask was closed with a cotton plug and aluminum foil to prevent the evaporation of methanol. The mixture was finally filtered in a Buchner funnel and then the filtrate was concentrated in a water bath at a temperature of 45 degrees Celsius to to obtain solid powder. The extract obtained was packaged in a storage bottle and stored in a desiccator.

Preliminary Physicochemical Evaluation of Tablets
The different brands of metformin tablets were subjected to different physicochemical tests such as friability, disintegration, dissolution, hardness, thickness and diameter, and weight uniformity tests. The drug quality assessment experiment was also done using

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pharmacopeia procedures described in the USP/NF 25, 2007.

Assay of Metformin

Quantities (20 tablets) of metformin were weighed and powdered; the quantity of the powder containing 0.1g of metformin was shaken with 70 mL of distilled water for 15 minutes and diluted to 100 mL with water. It was then filtered with a filter paper and the first 20 mL was discarded. 10 mL of the filtrate was diluted to 100 mL of water and 10 mL of the resulting solution was diluted to 100 mL with water. The absorbance of the resulting solution was taken at a maximum of wavelength of 232 nm. The content of the $C_4H_{11}N_5$, HCl taking at 798 as the value of A (1%, 1 cm) at the maximum at 232 nm was calculated (9)

Dissolution Test of Metformin Tablets alone

The dissolution of metformin was done according to the specification of (9). using the dissolution apparatus type II (paddle apparatus) at the rate of 100 rpm at 37 ± 0.5 ^{0}C for the six brands of metformin tablet, using the medium 900 ml of a 0.68% w/v solution of potassium dihydrogen orthophosphate and the pH was adjusted to 6.8 by the addition of 1M sodium hydroxide while rotating the basket at 100 revolutions per minute. About 10 ml of the sample was withdrawn and filtered. An equivalent volume of 10 ml was replaced as fresh fluid to maintain the sink condition. The absorbance of a layer of suitable thickness of the filtered sample was measured, using 'A UV-visible spectrophotometer (UV752)' at the maximum at 232 nm.

Dissolution test of Metformin tablet in the presence of *Artemisia annua*

The dissolution medium was heated to 37 ± 0.5 ^{0}C and 1 g of *Artemisia annua* extract was added to dissolution vessels (containing 500 ml of distilled water), and stirred with a glass rod. One tablet of metformin was then placed in the vessel and the dissolution vessel was immediately operated at 50 rpm for 15 minutes. Five sampling points (10, 20, 30. 40, and 50 minutes) were defined to monitor the dissolution. At each sampling point, a 10 ml solution 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 the analysis by UV spectrophotometry at 232 nm and the absorbance of each sample was taken.

Statistical analysis of the data obtained

Results were expressed as mean ± standard deviation using Microsoft Excel

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RESULTS

The result of the dissolution test of all the brands of metformin tablets (A-D) is indicated in table 1,and figure 1-6 Copmparative Dissolution profile of different brands of metformin alone and when combine with *Artemisia annua* (herbs)

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Table 1: Dissolution test for brand A, B, C, D and E (n = 5)

Brands	Percentage Drug released (%)				
	10 min	20 min	30 min	40 min	50 min
A	55.10	61.19	62.36	74.12	75.45
B	35.00	56.47	67.18	69.41	71.36
C	54.42	65.19	70.58	75.97	81.35
D	35.23	37.10	36.55	38.32	36.54
E	36.57	39.33	40.43	39.18	48.49

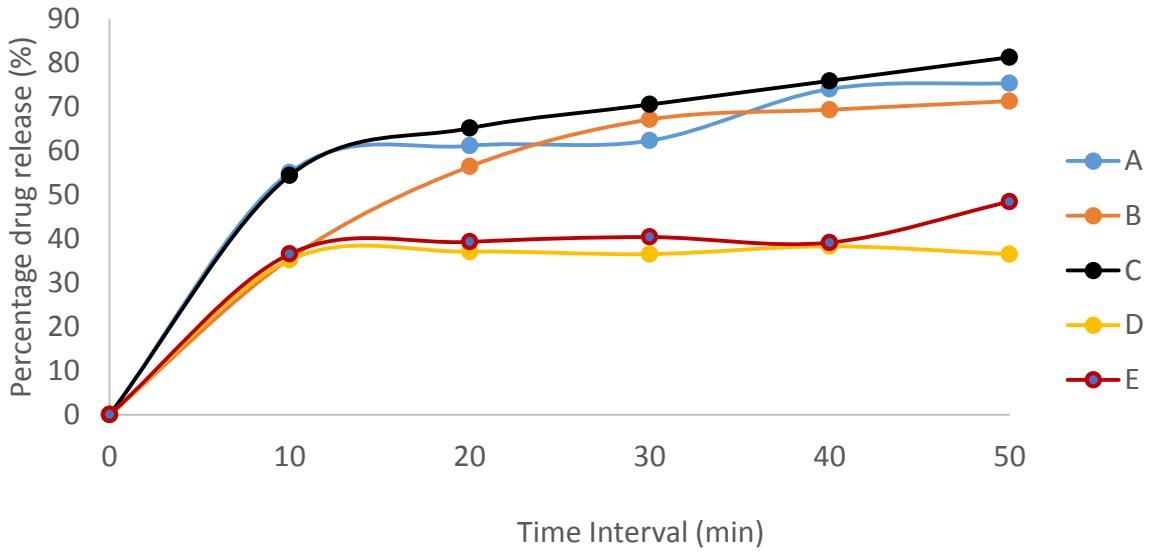

Figure 1: Dissolution profiles of five five different brands of metformin tablets

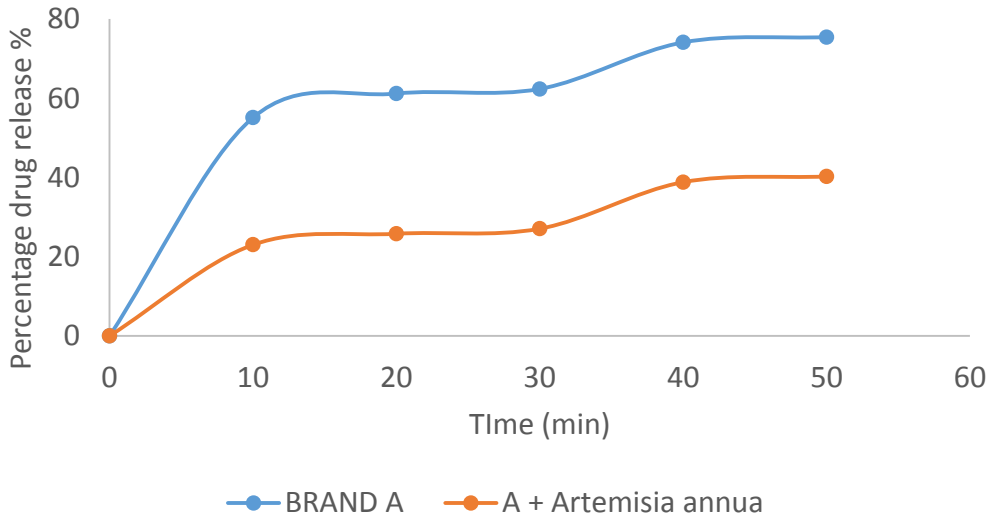

Figure 2: Copmparative Dissolution profile of brand A metformin alone and brand A metformin tablet with *Artemisia annua*

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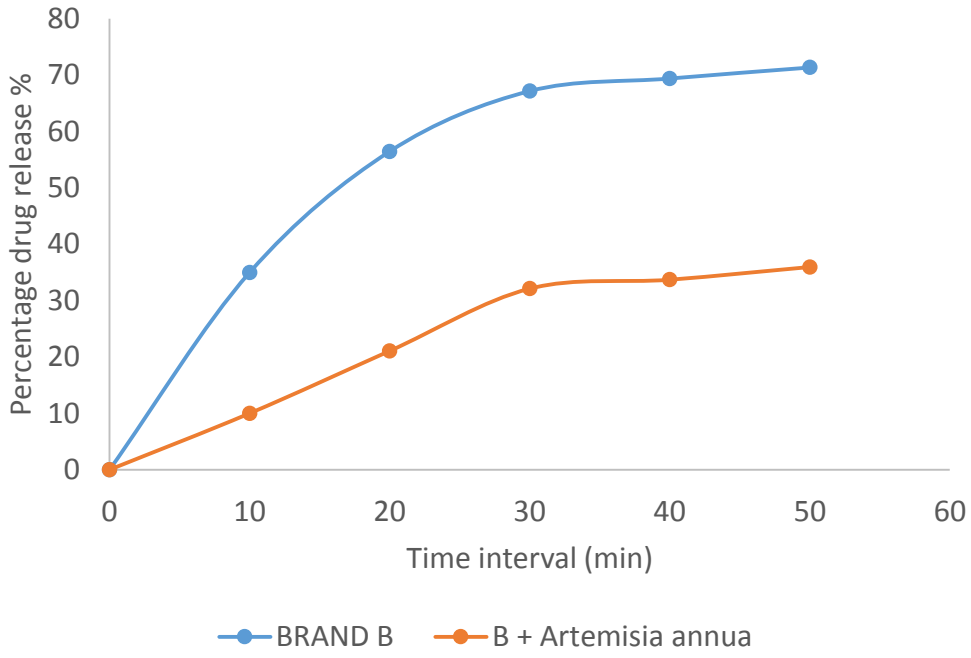

Figure 3: Dissolution profile of brand B only and brand B with *Artemisia annua*

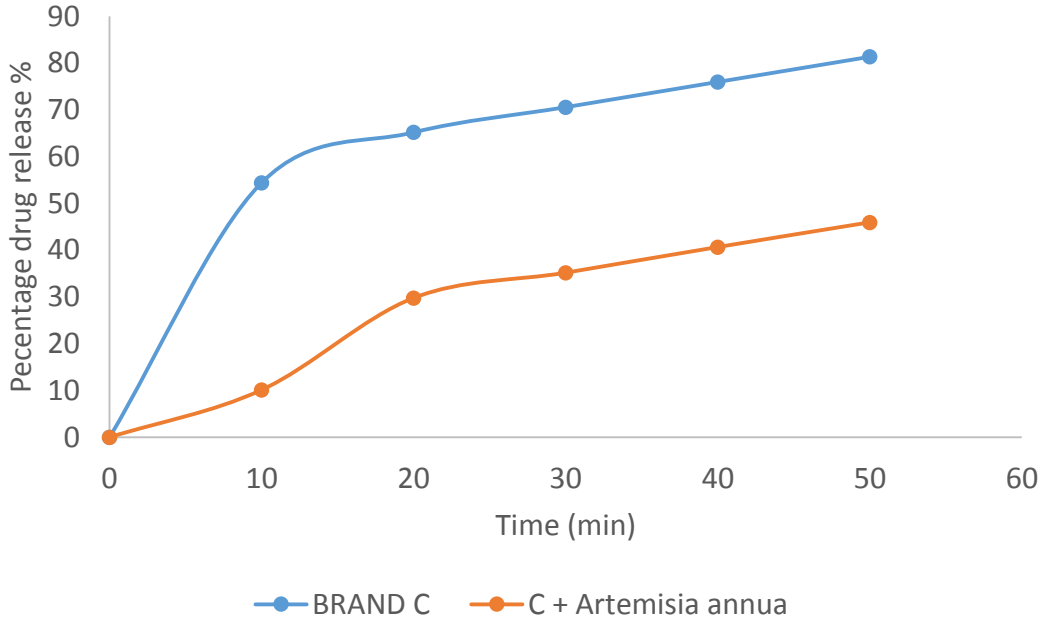

Figure 4: Comparative Dissolution profile of brand C metformin tablets alone and when ombine with *Artemisia annua*

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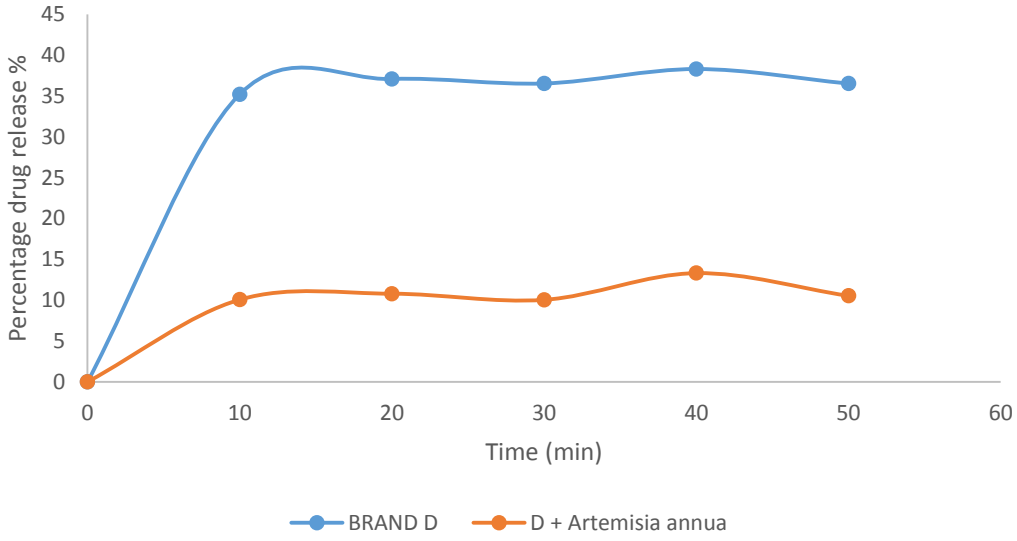

Figure 5: Dissolution profile of brand D only and brand D with *Artemisia annua*

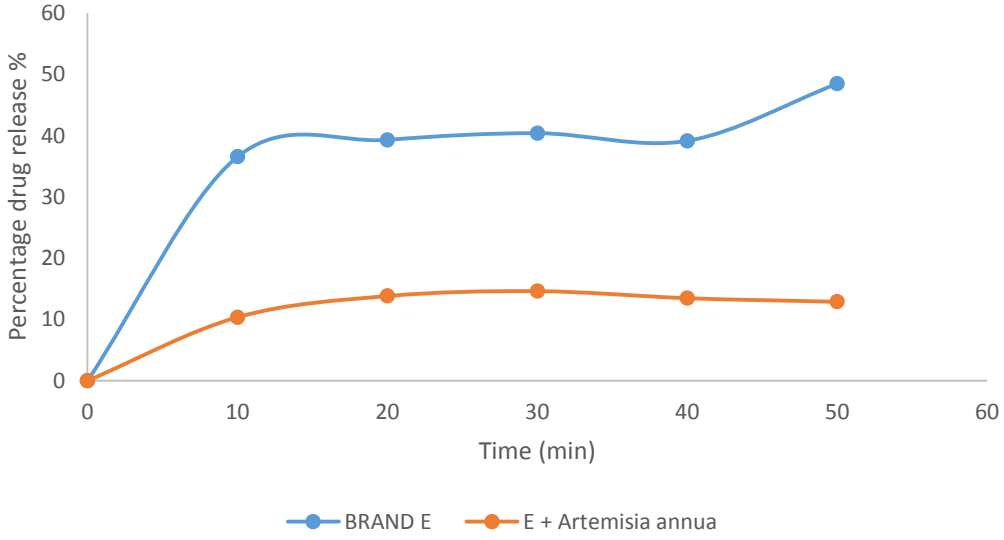

Figure 6: Comparative dissolution profile of brand E metformin alone and combination of brand E metformin with *Artemisia annua*

DISCUSSION

The drug oral solid dosage form (Tablet) only become available for absorption after undergoing disintegration and dissolution. Dissolution is employed to predict product behaviour *in-vivo* and also to establish the influence of manufacturing variables, including binder effect, mixing effect, granulation procedure and excipients type on solid dosage forms [8]. Dissolution is also employed as an *in-vitro* bioequivalence test to determine the equivalence/similarity or otherwise of solid dosage forms in which immediate release tablets should release ≥70 % of the prescribed amount in 45 min [9]. Results from the study revealed that brand A and C exhibited good dissolution profiles as immediate release tablets. The dissolution efficiency was determined for the tablet brands to ascertain their

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efficiency in releasing the drug to achieve their therapeutic activity. According to Anderson and others, the higher the dissolution efficiency, the more efficient the tablet is at releasing its embedded drug [10].

Dissolution and bioavailability of drugs can be influenced by the formulation elements and drug manufacturing procedures used. Tablets made using dry or wet granulation, or direct compression, may behave differently in test tubes and in living things. These elements directly impact the breakdown of dosage forms in gastrointestinal fluids, which in turn influences drug absorption (11). The *in-vitro* dissolution has shown that metformin and *Artemisia annua* interact in such a way that *Artemisia annua* lowers metformin's dissolution profile and subsequently its bioavailability. *Artemisia annua* may have absorbed or chelate metformin more effectively as a result of a variety of causes. First of all, flavonoids, alkaloids, and saponins are known to be present in *Artemisia annua*, which may be the cause of the interaction. Additionally, *Artemisia annua* trace minerals or elements like calcium, aluminium, magnesium, potassium, sodium, zinc, and copper, some of which are known to interact with medications by forming chelates. A syudy was carried out (12) that the antioxidant properties of *Artemisia annua* is linked to the phytochemicals present in it, especially flavonoids, gallic acid, and ellagic acids, which have the ability to scavenge free radicals Therefore, concomitant administration of metformin and *Artemisia annua* may reduce the bioavailability of metformin and also sub therapeutic effect.

CONCLUSION

The *in-vitro* dissolution study revealed that co-administration of metformin and *Artemisia annua* lowers the metformin's dissolution profile and subsequently its bioavailability. Thus, it is paramount to avoid concomitant administration of metformin and *Artemisia annua*.

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Conflict of Interest

Authors have decleared no conflict of interest

REFERENCES

1. Gong, L., Goswami, S., Kathleen, M. G., Russ, B. A., and Teri, E. K. (2012). Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenonics*; 22(11): 820-827
2. Ding Y, Jia Y, Song Y, Lu C, Li Y, and Chen M. (2014). The effect of lansoprazole, an OCT inhibitor, on metformin pharmacokinetics in healthy subjects. European Journal of Clinical Pharmacology, 70:141–6
3. Nies AT, Hofmann U, Resch C, Schaeffeler E, Rius M, and Schwab M. (2011). Proton pump inhibitors inhibit metformin uptake by organic cation transporters (OCTs). PloS One, 6:e22163.
4. Awortwe C, Bruckmueller H, and Cascorbi I. (2019). Interaction of herbal products with prescribed medications: A systematic review and meta-analysis. *Pharmacological Research*, *141*, 397–408

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5. Zhang G, Ma Y, Xi D, Rao Z, Sun X, and Wu X. (2019). Effect of high uric acid on the disposition of metformin: In vivo and in vitro studies. *Bio pharmaceutics and Drug Disposition*, *40*, 3–11.
6. Owuna G, Mustapha AA, Ogbonna CIC, Kaladi PH. (2013). Antimicrobial effects and Phytoconstituents of ethanol extract of leaves of *Artemisia annua* L. Journal of Medicinal Plants Studies, 1(5):97-101
7. Udem ND, Esimone OC and Adikwu MU. (2017). Effects of capsules of *V. amygdalina* combined with glibenclamide or metformin on blood glucose levels of diabetic rats. *International Journal of Pharmaceutics*; 44(1): 0976- 044.
8. Papadopoulou V, Valsami G, Dokoumetzidis A, Macheras P. (2018). Biopharmaceutics classification systems for new molecular entities (BCS-NMEs) and marketed drugs (BCS-MD): Theoretical basis and practical examples. *International Journal of Pharmaceutics*, 361(1-2):70-76.
9. British Pharmacopoeia. (2013). Her Majesty‘s Stationery Office, London, 2.
10. Anderson NH, Bauer M, Boussac N, KhanMalek R, Munden P, Sardaro M. (2013). An evaluation of fit factors and dissolution efficiency for the comparison of *in-vitro* dissolution profiles. J. Pharm. Biomed. Anal. 2013;17(4-5):811-22.
11. Oussama M and Mostafa I. (2016). Assessment of physicochemical properties of metformin hydrochloride (850mg) tablets marketed in Syria. *Journal of Chemical and Pharmaceutical Sciences:* V9I2 (0974-2115).
12. Kumar AP, Upadhyaya K. (2013). Preliminary phytochemical screening and physico-chemical parameters of *Artemisia absinthium* and *Artemisia annua*. Journal of Pharmacognosy and Phytochemicals, 1(6):229-235.