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Ruzu® Herbal Bitters and Glibenclamide Tablets: Dissolution and *In Vitro* Release Kinetics Studies

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Background: The concomitant intake of poly-herbal medicines with orthodox drugs raises huge concerns about herb-drug interactions and patient safety, especially as the pharmacokinetic properties of these herbal medicines are not known.
Objectives: This study aimed to determine the effect of Ruzu® herbal bitters on the dissolution profile and release kinetics of glibenclamide (Daonil®) in pH simulated dissolution media in order to predict possible herb-drug interaction.
Method: The assay of glibenclamide was carried out as described in the British Pharmacopeia (2014). *In vitro* dissolution of glibenclamide tablets was studied alone and with Ruzu® herbal bitters in phosphate buffer pH 6.8 using USP dissolution apparatus II at 75 rpm. Analysis of glibenclamide was done using High Performance Liquid chromatography coupled with a UV detector. Dissolution data were analysed and percentage glibenclamide released in the dissolution medium determined; dissolution data were compared using a model independent approach. Different mathematical models were adopted to explore the release kinetics.
Result: The glibenclamide tablets studied showed satisfactory drug content as per BP specifications. Ruzu® herbal bitters caused a significant reduction in the amount of glibenclamide released *in vitro* at gastrointestinal pH 6.8 ($P < 0.001$). The release of glibenclamide alone and with Ruzu® herbal bitters showed Higuchi mathematical model as their best fitting model.
Conclusion: Ruzu® Herbal Bitters significantly decreased the dissolution of glibenclamide tablets at gastrointestinal pH of 6.8. This could reflect on *in vivo* bioavailability performance with potential for causing sub-therapeutic levels of glibenclamide *in vivo*. Further studies are needed to assess herb-drug interaction *in vivo*.
Keywords: Glibenclamide; Ruzu herbal Bitters; Dissolution; Release Kinetics

INTRODUCTION

There has been a growing trend in the use of herbs to combat several disease conditions both in developed and developing countries (Djuv *et al.,* 2013). Millions of people currently use herbal therapies along with prescription and non-prescription medications (Duru *et a*l., 2016). Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially dangerous side effects and/or reduced benefits from the medications.

(Bushra *et al.,* 2011). The use of herbal medicines amongst patients with chronic diseases is well documented. In Nigeria, herbal medicines use is common amongst diabetic patients; they are used alone or with prescription drugs such as glibenclamide (Ezuruike and Prieto, 2014).
Among the herbal preparations gaining popularity in Nigeria is Ruzu® herbal bitters. It is a greenish brown solution with a characteristic bitter taste and ginger-like smell. According to the manufacturer's claim, Ruzu® herbal bitters is "Natures pure marvels" that has been proven by research to promote

digestion and aid in detoxification, promote loss of weight and useful in the management of high blood pressure and excess blood sugar. It contains *Uvarie chamae* 40% (Bush Banana), *Curculigo pilosa* 40% (Squirrel Groundnut) and *Colocythis citrullus* 20% (Bitter Apple) as the main constituents.

Glibenclamide is an oral hypoglycaemic agent of the sulphonylurea group used in the treatment of non-insulin dependent diabetes. It has a history of low bioavailability, which is attributed to its poor aqueous solubility and poor dissolution properties. It is chosen as the test drug substance on the basis of its low solubility. As a weak acid with pKa of 5.3 (Reynolds and Martindale, 1993), its solubility strongly depends on the pH, particle size and composition of the dissolution medium (Lobenberg *et al*., 2000).

Dissolution of drug in the solid dosage form into an aqueous medium is crucial for its absorption, with impact on its bioavailability and hence, therapeutic efficacy (Ayandokun *et al.,* 2016). If the conditions in the gastrointestinal tract are represented successfully in the experiments, dissolution tests can be prognostic of *in vivo* performance of drug products. In the case of immediate-release solid dosage forms such as tablets, dissolution tests can be used as a guide to assess the impact of certain changes in the formulation, manufacturing processes and dissolution media (O'Hara *et al*., 2008). Very often, an *in vitro* dissolution test is more sensitive and discriminating than an *in vivo* test (Fawzia *et al*., 2013).

Mathematical models have been used extensively for the representation of dissolution data (Polli *et al.,* 1997; Costa *et al.,* 2003). Some common models include: Higuchi, Hixson–Crowell, Korsmeyer–Peppas, zero-order, and first-order (Costa and Sousa, 2001). These mathematical models provide an insight into drug release mechanism and have been used to characterize dissolution profiles (Hossain *et al.,* 2016).

Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing around the world (Mohammad *et al.,* 2009). A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease. Resultant effects of such interaction include: drug toxicity or inefficacy and side/ adverse effects. Two well recognised mechanisms of drug interactions are: pharmacokinetics and pharmacodynamics (Barbara, 2006). Pharmacokinetic interactions result from alterations in a drug's absorption, distribution, metabolism, or excretion characteristics. These interactions affect drug action by quantitative alterations, either increasing or decreasing the amount of drug available to have an effect. Pharmacodynamics interactions are a result of the influence of combined treatment at a site of biological activity, producing altered pharmacological actions at standard plasma concentrations. Although drug interactions occur through a variety of mechanisms, the effects are the same: the potentiation or antagonism of the effects of drugs. Understanding the mechanisms underlying drug interactions is therefore important for the prediction and avoidance of drug toxicity when initiating combination therapy (Stephen *et al*., 2011).

This study thus sought to investigate the effect of Ruzu® Herbal bitters on the release cum dissolution profile of glibenclamide, and its clinical implications.

Material and Methods

Materials

Glibenclamide secondary standard was obtained from Nigeria German Chemical (NGC), Ogun state. Glibenclamide tablet 5mg and Ruzu® Herbal bitters were purchased from a registered community pharmacy premise in Lagos state. Both drugs were within the manufacturer's stipulated shelf-life.

Acetonitrile HPLC grade (Sigma-Aldrich®, USA), Methanol (Sigma-Aldrich®, USA), Concentrated Hydrochloric Acid (BDH®), Sodium Hydroxide pellets (Riedel-de-Haën®) and Potassium Dihydrogen Orthophosphate (SureChem®), were all obtained from the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Lagos.

Assay of Glibenclamide Tablet

The assay of glibenclamide tablet was carried out as specified in the British Pharmacopeia (BP) 2014. The recommended mobile phase by BP was employed. It comprised a mixture of potassium dihydrogen orthophosphate buffer (pH 3) and acetonitrile in a ratio of 53:47, respectively. The overall chromatographic run time was less than 5 min. The buffer was vacuum- filtered through 0.2 µm cellulose acetate membrane and then mixed with acetonitrile. The mobile phase was degassed in an ultrasonic bath. The column was set at room temperature and equilibrated to a stable base line prior to sample injections. The sample injection volume and flow rate was 20 µL and 1 mL/min respectively. The analytical wavelength was set at 300 nm.

Preparation of Standard Glibenclamide Stock Solution

50 mg of glibenclamide secondary standard was weighed and transferred into a 50 mL volumetric flask, 20 mL of methanol was added and the mixture sonicated for 20min. The volume was completed to 50 mL mark to obtain a final concentration of 1mg/mL (1000µg/mL) stock solution.

From the stock solution, a serial dilution of 100 µg/mL, 150 µg/mL, 200 µg/mL, 250 µg/mL and 300 µg/mL was prepared for the calibration curve.

Preparation of Calibration Solution

10 mg of standard Glibenclamide was weighed and dissolved in acetonitrile to obtain a 1mg/mL stock solution. From the stock solution, further dilutions were made using phosphate buffer pH 6.8 to obtain drug concentrations of 5 µg/mL, 10 µg/mL, 20 µg/mL, 50 µg/mL, and 100 µg/mL utilized to plot the calibration curve.

Preparation of Sample Solutions

This was done in accordance with BP (2014) specification. Six tablets of glibenclamide were accurately weighed and crushed. The equivalent of the average weight of one tablet was transferred to a 25 mL volumetric flask and dissolved with 2 mL of water. The volume was completed to mark with methanol. The mixture representing 200 µg/mL was then sonicated and filtered through a 0.45µm syringe filter. The prepared sample solution was injected two times along with double injections of a properly prepared standard solution of glibenclamide. The average value was used to calculate the sample concentration using the calibration curve. The percentage content of active ingredient was then calculated for the sample**.**

Preparation of Dissolution Media

Dissolution testing was carried out in Phosphate Buffer pH 6.8 prepared as stipulated in the BP (2014)

***In vitro* drug release studies**

Glibenclamide 5mg Tablet

The tests were performed according to USP (2013) specifications using Apparatus 2 (paddle method). The medium employed was 900 mL of 0.2M phosphate buffer (pH 6.8). Paddle rotation was set at 75 revolutions per min. Medium temperature was set at 37°C ± 0.5°C. Six tablets of Glibenclamide were evaluated.

Samples (5 mL) were withdrawn at pre-determined time points (5, 15, 30, 45, 60 and 90 min respectively) and replaced with 5 mL of the dissolution medium. All samples were filtered with the aid of a 0.45µm syringe filter and stored in a sample bottle before being injected into the HPLC column for analysis. The concentration of each sample was determined from the Glibenclamide standard calibration curve.

Glibenclamide 5mg tablet with Ruzu® Herbal bitters.

The media employed was 0.2M phosphate buffer (pH 6.8). In each dissolution vessel containing 860 mL of dissolution medium, one 5mg Glibenclamide tablet was introduced together with 40 mL of Ruzu® Herbal bitters, the poly-herbal formulation. At predetermined time intervals (5, 15, 30, 45, and 60, 90 mins respectively), 5 mL aliquot samples were withdrawn and replaced with 5 mL of the dissolution medium. The withdrawn samples were filtered thrice using 0.45µm Millipore filter for HPLC analysis as done above.

Chromatographic Conditions

Chromatographic separation was performed at ambient temperature on Agilent™ 1260 Infinity series with a reverse phase Zobrax Eclipse XDB C-18 (150mm X 4.6mm, 5µm) column, quaternary pump with auto sampler injector set at 20 µL. The mobile phase consists of acetonitrile and potassium dihydrogen phosphate in the ratio of 60:40. The flow rate of mobile phase was adjusted to 1.0 mL/min; UV detector wavelength was set at 300 nm. The mobile phase was filtered using a filtration unit coupled with a suction pump.

Kinetic modeling of drug release

The drug release data were fitted to various models like Higuchi's model (cumulative percent release against square root to time), Zero order model (cumulative percent release against time), First order model (log cumulative percent release against time) and Krosmeyer's peppas model (log cumulative percent release against log time) Hixson crowell (cubeth root of % drug remained against time) kinetics to know the release mechanism. The model fitting for the drug release for the samples were calculated by using Disso software PCP Disso V3 software (Singh & Singh, 1998).

The regression analysis was performed as follows: Zero-order (Q_t versus t), first-order (Log Q_t versus t), Higuchi (Q_t versus square root of t), Korsmeyer-Peppas (Log%Q_t versus Log%t), Hixson-Crowell (Q_t versus cube root of t); Where Q_t is the amount of Glibenclamide released at time t. The criteria for selecting the most appropriate model were sum of square of the residuals (SSR).

Statistical analysis

Results were expressed as mean ± SEM. Unpaired t-test was used to evaluate the percentage release of glibenclamide in the presence and absence of Ruzu herbal bitters® employing GraphPad Prism 6.0 software (La Jolla, CA). Dissolution profiles were analyzed using dissolution efficiencies (DE), calculated using the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time as shown in Equation 1.

$$DE = \{ \int_{t1}^{t2} y.dt / \ y_{100} * (t_2 - t_1)\} * 100 \quad \text{Equation 1}$$

where y is the percentage of drug dissolved at time t. The integral of the numerator which is the area under the curve was calculated using the trapezoidal method shown Equation 2.

$$AUC = \sum_{i=n}^{i=1} \frac{(t_1 - t_{i-1})(y_{i-1} + y_i)}{\quad} \quad \text{Equation 2}$$

RESULTS

Dissolution Profiles

The percentage glibenclamide released and dissolution efficiency when evaluated alone and with Ruzu® herbal bitters is represented in Table 1. Fig. 1 shows the dissolution profiles of glibenclamide tablets alone and with Ruzu® herbal bitters at pH 6.8. The results showed that the percentage glibenclamide released and the dissolution efficiency in phosphate buffer (pH 6.8) was lower in the presence of Ruzu® herbal bitters.

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Table 1: Statistical analysis of dissolution data showing percentage of glibenclamide released and dissolution efficiency (DE)

Time	Sample	% Released (Mean ± SEM)	% DE
5	Gli	4.47 ± 0.42	2.2371
	Gli+Ruzu	3.51 ± 0.33	1.7726
15	Gli	7.09 ± 0.38	4.5991
	Gli+Ruzu	3.55 ± 0.31	2.9416
30	Gli	10.29 ± 0.69	6.6431
	Gli+Ruzu	3.59 ± 0.50	3.2445
45	Gli	12.05 ± 0.35	8.1518
	Gli+Ruzu	5.04 ± 0.92	3.6003
60	Gli	15.36 ± 0.87	9.5412
	Gli+Ruzu	6.23 ± 0.87	4.1082
90	Gli	17.42 ± 0.88	11.8253
	Gli+Ruzu	9.90 ± 0.89	5.4269

n = 6, SD= standard deviation, SEM= standard error of mean, DE= Dissolution efficiency

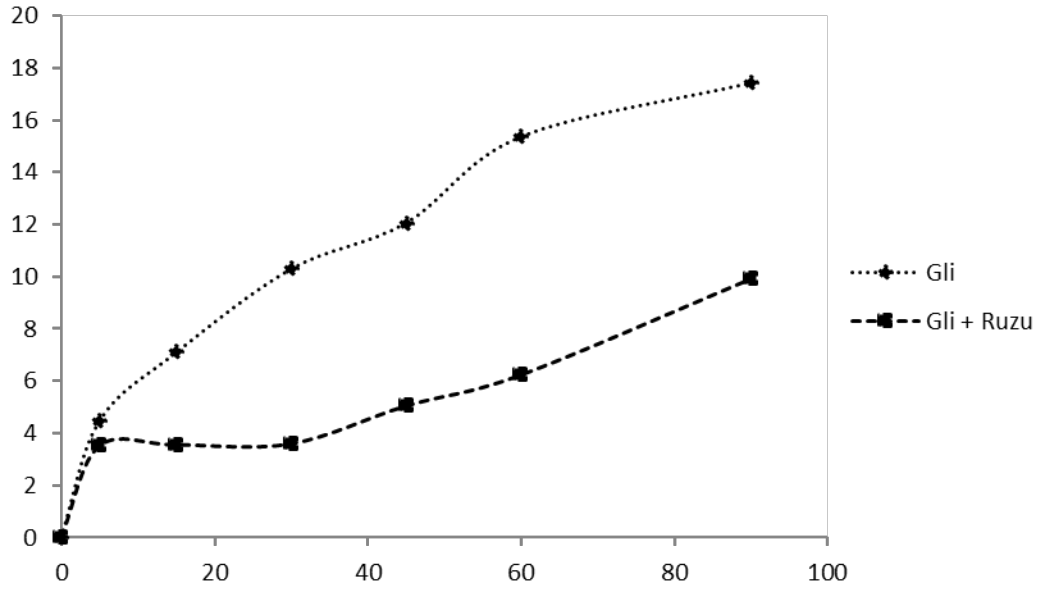

Figure 1: Dissolution profile of Glibenclamide tablets alone and with Ruzu® herbal bitters at pH 6.8

Drug release kinetics study

The results for the various models used to evaluate Glibenclamide release alone and with Ruzu® herbal bitters are shown in Tables 2 – 5 below. Release kinetics showed that glibenclamide release followed all the mathematical models; with Higuchi model as the best fit model. Glibenclamide release in the herbal bitters followed Higuchi model alone.

Table 2: Model Fitting (Average) of Glibenclamide Alone - Best fit model: Higuchi Model (Matrix)

	R	**K**
Zero order	0.8525	0.2332
T-test	3.647	(Passed)
1st order	0.8744	-0.0025
T-test	4.029	(Passed)
Higuchi Model (Matrix)	0.9807	1.8732
T-test	11.220	(Passed)
Peppas	0.9760	2.0409
T-test	10.019	(Passed)
Hix.Crow.	0.8674	-0.0008
T-test	3.898	(Passed)

T-table at P value = 0.05 (Two tails), DF = n – 2:-2.571

Table 3: Model fitting: Residual Sum of Squares of Glibenclamide alone

RESULTS				Zero	1st order	Matrix	Peppas	Hix.Crow.
Sr.No.	Time	Avg. %R	SD	52	42	1	2	45
1	0	0.000	0.00	0.000	0.000	0.000	-	0.000
2	5	4.474	1.04	10.943	10.346	0.082	0.000	10.549
3	15	7.086	0.95	12.870	11.291	0.028	0.312	11.818
4	30	10.288	1.71	10.831	8.853	0.001	0.186	9.495
5	45	12.051	0.87	2.418	1.650	0.265	1.026	1.888
6	60	15.368	2.15	1.888	1.632	0.737	0.114	1.714
7	90	17.419	2.17	12.760	8.726	0.124	0.807	9.895

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Table 4: Model Fitting (Average) of glibenclamide with Ruzu® herbal bitters with Model Fitting - Best fit model: Higuchi Model (Matrix)

	R	K
Zero order	0.7152	0.1122
T-test	2.288	(Failed)
1st order	0.7304	-0.0012
T-test	2.391	(Failed)
Matrix	0.8298	0.8862
T-test	3.325	(Passed)
Peppas	0.6318	1.8114
T-test	1.823	(Failed)
Hix.Crow.	0.7256	-0.0004
T-test	2.358	(Failed)

T-Table at P-value = 0.05 (Two Tails), DF = n-2:-2.571

Table 5: Model fitting: Residual Sum of Squares of Glibenclamide + Ruzu® Herbal bitters.

RESULTS				Zero	1st order	Matrix	Peppas	Hix.Crow.
Sr.No.	Time	Avg. %R	SD	13	12	8	11	12
1	0	0.000	0.00	0.000	0.000	0.000	-	0.000
2	5	3.545	0.82	8.905	8.769	2.445	0.319	8.815
3	15	3.507	0.77	3.326	3.115	0.006	0.462	3.186
4	30	3.588	1.24	0.049	0.018	1.603	2.561	0.027
5	45	5.036	2.28	0.000	0.010	0.826	0.715	0.005
6	60	6.228	2.15	0.255	0.314	0.405	0.040	0.293
7	90	9.901	2.18	0.040	0.011	2.231	6.826	0.019

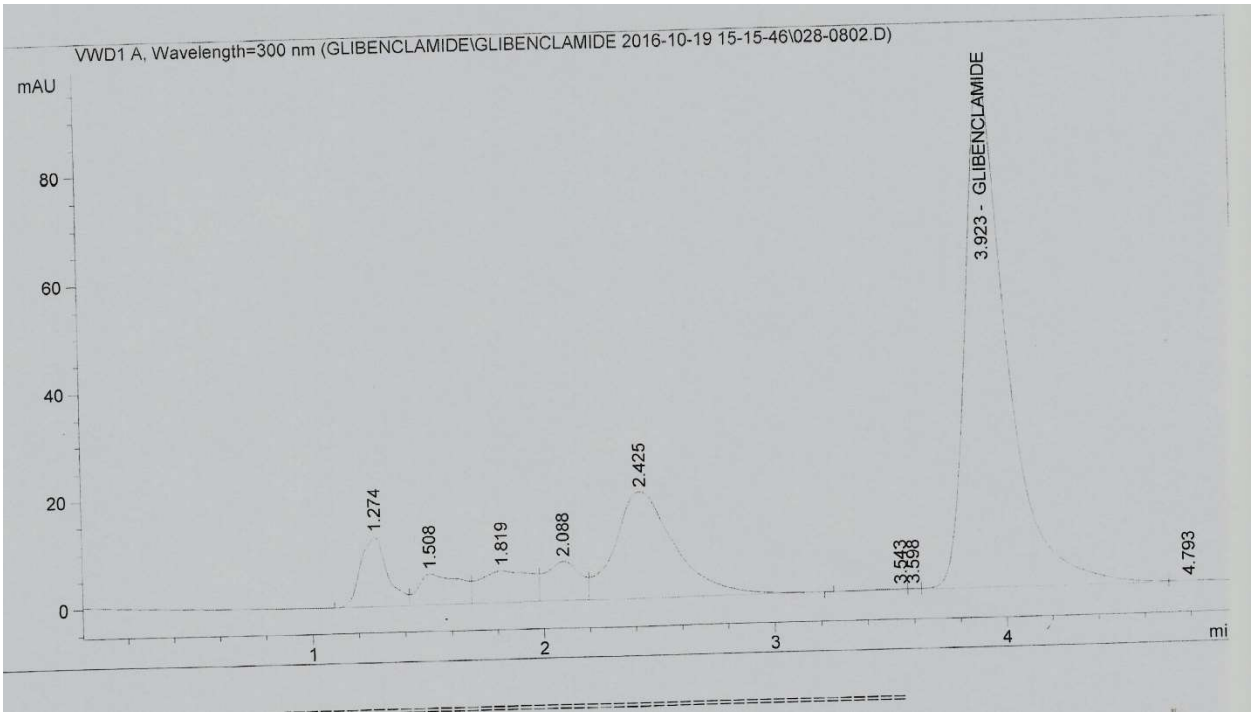

Fig 2: HPLC chromatogram of Glibenclamide tablets

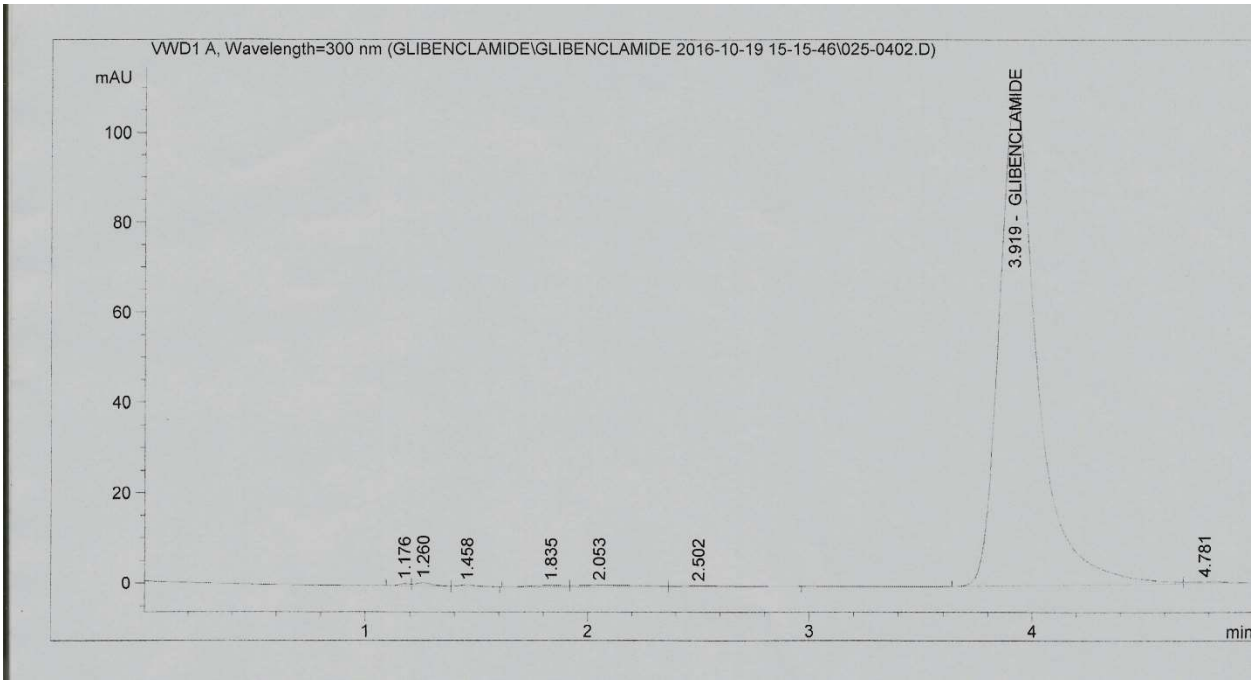

Fig. 3: HPLC Chromatogram of Glibenclamide standard

DISCUSSION

The prevalence of orthodox and herbal medicine combination is widely and rapidly growing even among patients with diabetes (Duru *et a*l., 2016). Consequently, herb-drug interactions have become a subject of particular interest arising from numerous reports that have been made about such interactions mediated by different mechanisms. (Akinleye *et al.,* 2016).

Ruzu® herbal bitters is a popular product in Nigeria, with claims of efficacy in managing and treating conditions such as: diabetes, weak erection, typhoid and malaria, vaginal discharge, menstruation anomalies, high blood pressure, etc. Considering such grandiose claims for these herbal remedies and the fact that they are used concomitantly with orthodox medicines, assessment of potential interaction of these herbals with concomitantly administered drugs is thus very timely to ensure patient safety and achievement of therapeutic outcomes.

In the assay of glibenclamide tablets, the peak of the analyte in the chromatogram of the solution (Fig. 2) prepared from the tablets was confirmed by comparing the retention time (3.9 min) with that of a standard solution of glibenclamide as shown in Fig 3. A reasonable peak shape was obtained for the analyte. BP (2014) requires Glibenclamide tablets to contain not less than 95% and not more than 105% of the claimed amount. The tested tablets being on the borderline 95.4% passed the assay. It was concluded that the glibenclamide tablets used for this study demonstrated generally satisfactory assay result.

Drug dissolution is a time-dependent process that represents the final step of drug release (from a dosage form), which is ultimately required before a drug can be absorbed or exert a pharmacological action. For immediate release dosage forms, the rate of drug release and dissolution relative to the rate of transit through the intestine, and the permeability profile of the small intestine determine the rate and extent of drug absorption (Sinko, 2006). In other words, before a drug can be absorbed to exert action, it must go through liberation from the dosage form and release into a bio-medium. *In vitro* dissolution tests are often used to predict *in vivo* drug performance due to the critical nature of release of drug from the dosage form and dissolution under physiological conditions (Emam, 2006). The release of glibenclamide was evaluated with and without the herbal bitters studied.

The dissolution profile obtained for glibenclamide alone and in the presence of Ruzu bitters® is shown in Figure 1. From the figure, it was observed that glibenclamide alone and with Ruzu bitters in the dissolution medium did not release significant percentage of the drug within 90 minutes. In fact, only 17.4% of glibenclamide was released within 90 minutes; and with Ruzu bitters only 9.90% of Glibenclamide was released; showing an obvious reduction in the release of glibenclamide, which was statistically significant (P-value = 0.027). The results of glibenclamide tablets dissolution obtained from this study however, are in consonance with previously reported studies. El-sabawi *et al.,* (2013) reported less than 20% release of glibenclamide within 90 min. The dissolution of glibenclamide has been shown to increase significantly (from approximately 20 - 90%) by changing the pH by one unit only (from 6.8 to 7.8), which indicates the high sensitivity of glibenclamide solubility to pH of the medium. Another study on the originator, Euglucon N® which is the trade name of glibenclamide in Britain (made by Boehringer Mannheim/Hoechst, Germany), showed that no more than approximately 20% of the drug was released over 90 min in simple phosphate buffer (pH 6) (Löbenberg *et al.,* 2000). Comparison of the performance of Daonil® (Hoechst) in phosphate buffer (pH 7.4) was just below 40% over 1 hour (Lee *et al*., 2010). However, significantly higher dissolution rates were obtained when dissolution was studied in simulated fluids (Tashtoush *et al*., 2012).

Mathematical modeling increases understanding of drug release mechanism and in turn helps to identify possible drug interactions (Hossain *et al.,* 2016). The parameters of the mathematical models explored in this study are shown in Tables 2 and 4. Tables 3 and 5 represent the descriptive statistics of regression for the dissolution data which were calculated based on the average mean dissolution data curve, including determination coefficient (R) and the residual sum of squares. The statistics of glibenclamide alone fits into all the mathematical models (Zero-order, First-order, Hixson-Crowell, Korsmeyer-Peppas); while Glibenclamide with Ruzu® herbal bitters did not fit into all of the mathematical models except for Higuchi model. The aforementioned mathematical models are diffusion based release mechanism with the exception of Hixson-Crowell (erosion release mechanism) (Hina *et al.,* 2015). This indicates that the release mechanism of glibenclamide into the dissolution medium is predominantly diffusion based and partly by erosion. The presence of Ruzu herbal bitters in the dissolution media resulted to a change in the efficiency of the release mechanism from predominantly diffusion based mechanism involving all the models to just Higuchi release model. The selection of the best fitting model is based on the descriptive statistics of the regression in the following order: higher determination coefficient, smaller the residual sum of squares. For the

dissolution curves up to 90 minutes, the best fit model for the studied samples overall is the matrix (Higuchi) model. Therefore, glibenclamide with Ruzu® herbal bitters exhibit the Higuchi release kinetics as with glibenclamide alone. This implies that the release of glibenclamide from the dosage form generally follows diffusion to transport drug from the dosage matrix into the *in vitro* study fluid depending on the concentration gradient between the dosage form and the *in vitro* fluid (Base *et al.,* 2013). Assessment of the effect of Ruzu® herbal bitters on the *in vitro* release of glibenclamide at the simulated intestinal pH 6.8 revealed a significant reduction in drug release. This was evidenced by the decrease in the percentage of glibenclamide released in the presence of Ruzu® herbal bitters compared to percentage release of the drug alone. Since a drug has to dissolve into solution before it can be absorbed, this decreased drug release implies a reduction of drug molecules available for absorption to ignite a therapeutic response. Further evaluation of the dissolution profiles of glibenclamide alone and with Ruzu® herbal bitters (Table 1) using dissolution efficiency showed significant difference in dissolution efficiency (DE). Where two profiles of different brands are evaluated, a difference in DE of less than 10% is assumed to indicate bioequivalence (Ilomuanya *et al.,* 2015). This again shows inconsistency in the release characteristics of glibenclamide alone and with Ruzu® herbal bitters. The observed decrease in the dissolution of glibenclamide in this study could inhibit bioavailability, resulting in sub-therapeutic concentrations of the drug in systemic circulation. Overall, glibenclamide with Ruzu® herbal bitters exhibited dissolution profiles that are significantly different from that of glibenclamide alone. The decrease in the release of glibenclamide observed in the presence of Ruzu® herbal bitters could possibly lead to poor therapeutic outcome of the drug for the management of hyperglycemia in diabetics. This could result to an increased risk of micro and macro vascular complications caused by high plasma blood glucose concentration with consequent morbidity and mortality. This reduction in glibenclamide dissolution in the presence of Ruzu® herbal bitters also touch on the potential for drug interaction when these two medications are used concomitantly. Care should therefore be taken in using these two drugs concomitantly. Healthcare practitioners should be well informed about potential herb-drug interactions and patients counselled appropriately.

Conclusion

The dissolution behaviors of Glibenclamide tablets with Ruzu® herbal bitters in phosphate buffer (pH 6.8) showed a lower percentage release of the drug compared to Glibenclamide alone. These disparities in dissolution profiles are likely to reflect potential differences in clinical performance when taken concomitantly with Ruzu® herbal bitters. Properly controlled *in vivo* studies in animals and possibly humans are strongly recommended to ascertain the significance of these differences observed *in vitro*.

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