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In vitro study of the interaction between artemether-lumefantrine and ciprofloxacin/metronidazole

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Abstract

This study investigated the *in vitro* interactions between artemether-lumefantrine and ciprofloxacin or metronidazole in their co-administration. Commercial brands of artemether-lumefantrine, ciprofloxacin and metronidazole tablets were evaluated for some physical properties such as organoleptics, dimensions, weight uniformity, crushing strength and friability. The effects of their interactions on the disintegration times and drug release profiles of artemether-lumefantrine, metronidazole, and ciprofloxacin tablets were investigated. Interaction studies using Fourier transform infra-red (FTIR) analysis were also carried out. All the commercial brands of tablets used in the study met BP specifications in their weight uniformity, friability (≤ 1.0%), and crushing strengths (5.0 - 12.0 kgF). There was no significant ($p \geq 0.05$) effect on the disintegration times of artemether-lumefantrine tablet in the presence of ciprofloxacin or metronidazole and vice versa. However, there was significant ($p \leq 0.05$) retardation of artemether-lumefantrine release in the presence of ciprofloxacin or metronidazole. FTIR analysis showed no appreciable shift in spectral bands of artemether-lumefantrine in the presence of ciprofloxacin or metronidazole. The *in vitro* interaction between tablet formulations of artemether-lumefantrine and ciprofloxacin or metronidazole and vice versa, showed that a more drug release retardation is seen between artemether-lumefantrine and metronidazole than with ciprofloxacin and these changes in drug release indicated an absorption interaction, possibly due to alteration in gastric pH.

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INTRODUCTION

Artemether-lumefantrine (AL) is an artemisinin combination therapy (ACT) used in the treatment of uncomplicated *Plasmodium falciparum* malaria and widely prescribed across sub-Saharan Africa (WHO, 2015; Abamecha *et al.*, 2021). It may be used as a co-prescription in cases of malaria co-morbidities. Ciprofloxacin is a fluoroquinolone antibiotic that is used to treat different types of bacterial infections while metronidazole is considered to be an antiprotozoal, anti-bacterial and anti-parasitic agent used in the management of amoebiasis/giardiasis (Gonzales *et al.*, 2019; Pham *et al.*, 2019).

The co-prescribing of artemether-lumefantrine and an antibacterial agent is becoming a common practice in the treatment of malaria and enteric fever co-infection (Sumer *et al.*, 2014; Fomba *et al.*, 2020). The co-administration of two or more drugs is usually the cause of drug-drug interactions (DDI) with its consequent therapeutic implications ranging from physical and chemical antagonism, alteration, synergism, or potentiation. DDIs affect the pharmacokinetics or pharmacodynamics of drugs by altering the rates and extents of the drug's absorption, distribution, metabolism and excretion (Brody, 2018).

Studies have shown that one potential influence for DDI stems from patients' perceptions or attitudes toward malarial treatment. Patients demand other drugs mostly antibiotics because they believe that antibiotics are taken with antimalarial as a preventive measure for other infections (Ntamabyaliro *et al.*, 2018; Jimam *et al.*, 2019). Another influence on DDI is the presumptive treatment by prescribers based on a syndromic approach or clinical symptom without laboratory contributing to polypharmacy and increased risk of DDIs diagnosis (Uzochukwu *et al.*, 2010; Ezenduka *et al.*, 2014; Oyinaka *et al.*, 2021). The *in vitro* drug-drug interaction studies have been used to predict the *in vivo* interactions of co-administered drugs and a number of in vitro models have been developed (Wienkers and Heath, 2005; Peng *et al.*, 2021; Han *et al.*, 2022). One of such model is the Fourier transform infra-red (FTIR) spectroscopy, an instrumental method that uses spectra wave interference on the basis that molecules have a characteristic infra-red spectrum. This study aims to investigate any possible drug-drug interaction between artemether-lumefantrine and ciprofloxacin or metronidazole tablets on concomitant administration and the impact of the interaction on the disintegration times and drug release profiles of the tablets.

MATERIALS AND METHODS

Artemether and lumefantrine powders were gifts from Edo Pharmaceutical Ltd, Benin City, Edo State, Nigeria, ciprofloxacin hydrochloride powder (May and Baker, Nigeria), metronidazole powder (William Ransom and Son PLC, Hitchin Hertfordshire, England), concentrated hydrochloric acid and ethanol (BDH Chemicals, Poole, U.K.). Coartem®-artemether/lumefantrine 20/120 mg (Novartis Pharma AG, Switzerland), Cenox® - ciprofloxacin hydrochloride 500 mg (Elbe Pharma Nig. Ltd., Nigeria), and Femagyl® - metronidazole 200 mg (Pharmatex Ind. Ltd., Nigeria) tablets were purchased from a local pharmacy in Benin City.

Assessment of tablets

The commercial brands of tablets (Coartem®, Cenox®, and Famagyl®) purchased were evaluated for their physiochemical properties using standard procedures (BP, 2009).

Physical inspection

The primary and secondary packs of the tablets were inspected for tampering and their label information such as manufacturer/country of origin, expiry date, batch and NAFDAC (National Agency for Food and Drug Administration and Control) numbers were recorded.

Organoleptic properties

Some organoleptic characteristics (colour, texture, odour, and taste) of the tablets were assessed by ten (10) individuals and a matching response of a majority (8 out of 10) of the persons was recorded.

Dimension

Ten tablets per brand were assessed for thickness and diameter using a digital Vernier caliper (Mituloyo 500-196-30, Japan), and their average and as well as standard deviation values, computed and recorded.

Weight uniformity

The weight of twenty (20) randomly selected tablets per brand were individually taken (Tianfu - DT-1000, China) and their average weights and standard deviations calculated and recorded.

Friability

Ten (10) randomly selected tablets from each brand were weighed together and deposited in the drum of a friabilator (Erweka GmbH, Germany) operated at 25 rpm for 4 min. The tablets were brought out of the drum and brushed, to remove all particles from the tablet's surfaces before being re-weighed. The tablet's percentage loss in weight was calculated.

Crushing strength

The force required to crush each of ten tablets per brand was assessed with a digital tablet hardness test apparatus (Campbell Electronics, Mumbai, India) by diametrically compressing the tablets. Their mean crushing strength values and standard deviations were calculated.

Interaction studies

Disintegration time test

Six tablets per brand were assessed of their disintegration times in 500 ml of 0.1 N HCl solutions at 37 ± 0.5°C with a BP disintegration apparatus (MK IV. Manesty Machines Ltd, UK). Various disintegration media consisting of a dispersion of one (1) tablet of ciprofloxacin (Cenox®), two (2) tablets of metronidazole (Famagyl®) and four (4) tablets of artemether-lumefantrine (Coartem®) in 500 ml of 0.1 N HCl solution were prepared separately and used in testing the effect of each of the brands on the disintegration time of the other brands.

In order to test the effects of the presence of ciprofloxacin or metronidazole tablets on the disintegration times of artemether-lumefantrine tablets, the disintegration time test was conducted with six tablets of artemether-lumefantrine using the medium containing dispersed ciprofloxacin tablet and another six tablets used with the medium containing two dispersed tablets of metronidazole. The same procedure was repeated for six tablets each of ciprofloxacin or metronidazole using the medium containing dispersions of artemether-lumefantrine tablets.

Dissolution test

Calibration curves of artemether and lumefantrine

Serial dilutions of artemether and lumefantrine ranging from 10-100 µg/ml were prepared separately from stock solutions containing 1.0 mg/ml in 0.1 N HCl/10% ethanol (1:9). The absorbances of the dilutions were read with a spectrophotometer (T70, PG Instruments Ltd, UK) at 212 and 234 nm for artemether and lumefantrine respectively, against a blank of 0.1 N HCl/10% ethanol. Their recorded absorbances were used in plotting their lines of regression and generation of their respective regression equation.

Calibration curves of ciprofloxacin and metronidazole

Standard stock solutions of ciprofloxacin hydrochloride and metronidazole containing 1.0 mg/ml in 0.1 N HCl were subjected to serial dilutions to obtain a concentration range of 1.0 to 100 µg/ml. Absorbances of the dilutions were taken at 287 and 275 nm for ciprofloxacin and metronidazole, respectively against a 0.1 N HCl solution blank. Their absorbances were plotted against their corresponding concentrations to obtain their respective calibration curves and generation of equations.

Dissolution profiles of tablets

Dissolution tests of the tablets (Coartem®, Cenox®, and Famagyl®) were carried out with a BP dissolution apparatus (Caleva ST7, GB Caleva. UK) containing 900 ml of 0.1 N HCl solutions held at 37 ± 1.0°C and a basket rotation of 50 rpm. With the apparatus operated for 60 min, 5.0 ml aliquots were taken at

determined time intervals from the dissolution fluid and replaced with same volume of fresh fluid held at same temperature. The samples taken were filtered and their absorbances read. The amount of drug released at each determined time interval was calculated with the equation generated from the calibration plot of the pure drug sample.

Dissolution profile of artemether-lumefantrine tablets in the presence of ciprofloxacin or metronidazole

Dissolution tests of Coartem® tablets were carried out in 900 ml of 0.1 N HCl solution containing a dispersed tablet of ciprofloxacin (Cenox®) or two tablets of metronidazole (Famagyl®). Withdrawn samples were spectrophotometrically analyzed separately at 212 and 234 nm for artemether and lumefantrine respectively, against a blank of 0.1 N HCl solution. Their amounts and percentages of drug release at each time interval were calculated.

Dissolution profile of ciprofloxacin or metronidazole tablets in the presence of artemether-lumefantrine

Dissolution tests procedures were repeated with ciprofloxacin (Cenox®) or metronidazole (Famagyl®) tablets with same media (900 ml 0.1 N HCl solution containing four (4) dispersed tablets of artemether-lumefantrine (Coartem®)). Withdrawn samples were spectrophotometrically analyzed at 287 nm for ciprofloxacin and at 275 nm for metronidazole. Their amounts and percentages of drug release at each time interval were calculated.

FTIR spectroscopic analysis

The FTIR spectroscopic analysis was carried out using an FTIR-4100 Spectrophotometer (Shimadzu Co., Japan). Five (5) milligram powder of crushed artemether-lumefantrine tablet was blended with potassium bromide (KBr) powder and compressed into a 200 mg tablet. The tablet was scanned over a range of 4000 to 500 cm^{-1} wavenumbers. The process was repeated by blending 5.0 mg of pure ciprofloxacin or metronidazole powder with same quantity of artemether-lumefantrine powder before final mixing with KBr and compression into tablet.

Statistical analysis

Experimental results were computed and reported as mean ± standard deviations of triplicate determinations. Statistical differences between mean was computed with ANOVA, while $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

Result from the label information, organoleptic and physical evaluations of the tablet brands are shown in Table 1. The tablet packs were elegantly labelled bearing their brand names, batch numbers, manufacturing, and expiry dates, as well as their manufacturers and country of origin. They also had registration numbers from the National Agency for Food and Drug Administration and Control (NAFDAC), the country's drug regulatory agency. The tablets were yellow to white in colour, smooth to touch while their odour and taste ranged from unpleasant to odourless and bitter to tasteless, respectively. The tablet weight of individual brands was varied due to their varied sizes but their mean values ranged from 350.8 - 800.9 mg. Hardness and friability of the tablets were within the range of 5.74 - 12.11 kgF and 0.03 - 0.08%, respectively.

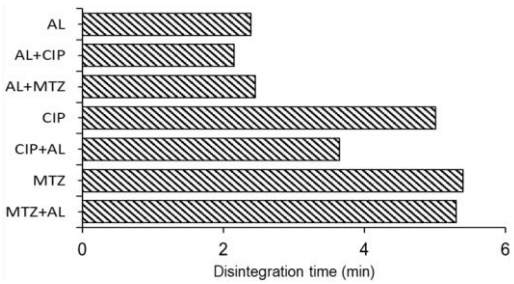

Fig. 1. Comparative disintegration time profiles of artemether-lumefantrine (AL), ciprofloxacin (CIP) and metronidazole (MTZ) tablets alone and in the presence of each other

The results from the disintegration time studies are shown in Fig. 1. The mean disintegration time for artemether-lumefantrine (Coartem®) tablets in 0.1 N HCl solution was 2.39 min. But with ciprofloxacin (Cenox®) tablets dispersed in the disintegration medium, the disintegration time became 2.15 min while with metronidazole (Famagyl®) tablets

dispersion, it gave a value of 2.45 min. Also, the disintegration time recorded for ciprofloxacin tablets was 5.01 min and in the presence of artemether-lumefantrine tablets, it gave 3.65 min. Likewise, the time recorded for metronidazole tablets was 5.4 min and it then gave 5.3 min in the presence of artemether-lumefantrine tablets.

Results from the dissolution studies of the tablets are shown in Figs 2a and b while some drug release parameters derived from their dissolution profiles are presented in Table 2. The artemether-lumefantrine (AL) tablets achieved a maximum drug release of 78.9% for artemether and 70.3% for lumefantrine within 60 min of dissolution testing. But in the presence of ciprofloxacin or metronidazole tablets dispersed in the dissolution medium, the AL tablets showed a maximum release of 62.0 or 34.7% for artemether and 58.5 or 38.5% for lumefantrine, respectively (Fig. 2a, Table 2). On the other hand, ciprofloxacin and metronidazole tablets showed a maximum percentage release of 83.8 and 80.7%, respectively within 60 min but both tablets exhibited a decreased drug release of 48.3 and 42.0%, respectively, in the presence of AL tablets dispersed in their dissolution media (Fig. 2b, Table 2).

Table 1. Physiochemical properties of the various brands of tablets (Mean ± SD, n = 3)

Tablet property	Artemether/lumefantrine	Ciprofloxacin	Metronidazole
Brand name	Coartem	Cenox	Famagyl
Batch number	KFH04	M1029	T2106
NAFDAC number	B4-0262	04-3002	B4-2277
Manufacturing date	03/2022	02/2021	05/2022
Expiry date	02/2024	01/2024	04/2025
Manufacturer/Origin	Novartis (Switzerland)	Elbe Pharma (Nigeria)	Pharmatex (Nigeria)
Colour	Yellow	White	White
Surface texture	Smooth	Smooth	Smooth
Odour	Unpleasant	Odourless	Slight
Taste	Bitter	Tasteless	Bitter
Weight (mg).	350.8 ± 0.51	800.9 ± 0.53	508.6 ± 0.70
Hardness (kgF)	5.74 ± 0.12	12.06 ± 0.20	12.11 ± 0.25
Diameter (mm)	10.08 ± 0.02	16.67 ± 0.02	11.1 ± 0.02
Thickness (mm)	3.60 ± 0.02	6.20 ± 0.06	5.16 ± 0.03
Friability (%)	0.08 ± 0.01	0.05 ± 0.02	0.03 ± 0.01

Table 2. Some drug release parameters of artemether, lumefantrine, ciprofloxacin and metronidazole in the various dissolution media

Drug	Drug release parameters				
	C_{40} (mg)	T_{70} (min)	C_{max} (%)	AUC (mg.min/ml)	DE
ART	14.27	36	78.87	297.7	1.00
ART + CIP	11.54	-	62.00	235.7	0.79
ART + MTZ	12.04	-	34.70	129.4	0.44
LUM	81.24	56	70.30	1632.0	1.00
LUM + CIP	63.00	-	58.50	1328.4	0.81
LUM + MTZ	39.00	-	38.50	848.4	0.52
CIP	381.65	34	83.86	7942.5	1.00
CIP + AL	238.50	-	48.30	4800.0	0.60
MTZ	126.60	38	80.70	2884.0	1.00
MTZ + AL	75.40	-	42.00	1557.0	0.54

NB: C40, T70, Cmax, AUC and DE are concentration of drug released within 40 min, time to achieve 70% dissolution, maximum drug released within 60 min, total drug released and dissolution efficiency, respectively.

The dissolution parameters showed that the AL tablets released 70% of its content of artemether in 36 min while the same percentage of lumefantrine was achieved in 56 min (Table 2). Neither artemether nor lumefantrine achieved up to 70% release in the presence of ciprofloxacin and metronidazole tablet

dispersion within 60 min. Similarly, ciprofloxacin and metronidazole tablets achieved 70% release within 34 and 38 min, respectively while both tablets failed to reach up to 50% drug release in the presence of AL dispersed tablets (Table 2).

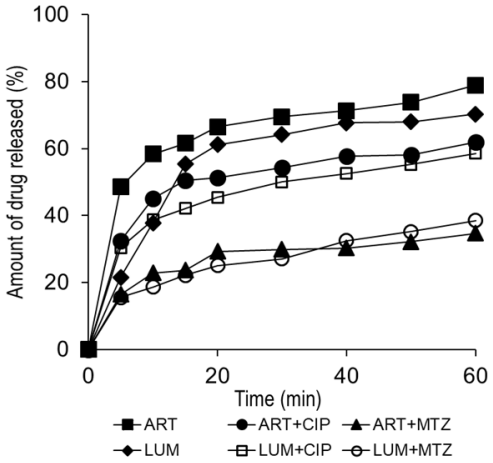

Fig. 2a. Release profiles of artemether and lumefantrine from AL tablets and in the ciprofloxacin (CIP) or metronidazole (MTZ)

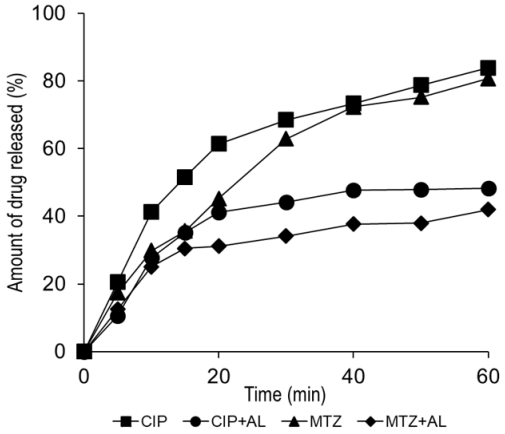

Fig. 2b. Release profile of ciprofloxacin (CIP) and metronidazole (MTZ) and in the presence of AL tablets

The spectra resulting from the FTIR analyses of AL tablet powder and its mixture with ciprofloxacin and metronidazole tablet powders are presented in Fig. 3. The peaks observed for AL alone were broad peaks between 3394.72-3462.54 cm-1 corresponding to the aliphatic -OH bending of artemether and lumefantrine moieties in the AL tablet. The spectral band also showed peaks at 2937.48 and 2951.09 cm-1 which corresponds to the aliphatic -CH stretching and bending vibrations due to artemether and lumefantrine, respectively. There were two broad peaks at 1462.04-1253.42 cm-1 corresponding to -CH stretching and at 890 - 820 cm-1, for the endoperoxide bridge (-C-O-O) of artemether. These spectral bands in comparison with those gotten from the mixture of AL tablets with ciprofloxacin and metronidazole tablets exhibited little or no shift, suggesting no interactions.

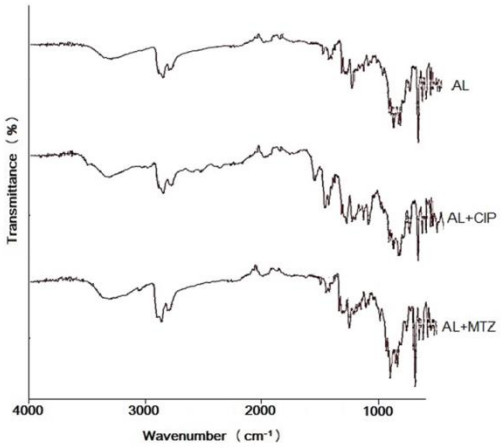

Fig. 3. Spectra of artemether-lumefantrine (AL) tablet and it physical mixture with ciprofloxacin (AL+CIP) and metronidazole (AL+MTZ) tablets

This *in vitro* interaction study between artemether-lumefantrine and ciprofloxacin or metronidazole tablets was carried out to determine any possible drug-drug interaction with the concomitant oral administration of these drugs. The tablets that were purchased and used for the study exhibited satisfactory physical parameters in their weights, hardness, and friability, as their values fell within the acceptable limits of the British Pharmacopoeia specifications (BP, 2009). These satisfactory results may be due to the fact that the brands used in the investigation are common brands and have undergone the required registration process of the country's regulatory agency (NAFDAC).

Results from the disintegration time test revealed that all the tablet brands disintegrated within 5.0 min, as conventional tablets and hence meet the 15 min

stipulated disintegration time for immediate release tablets by the British Pharmacopeia (BP, 2009). However, no significant effect ($p > 0.05$) was observed between the disintegration times of artemether-lumefantrine tablets in 0.1 N HCl medium and in the presence of either ciprofloxacin or metronidazole tablets dispersed in the disintegrating medium. This same non-significant observation was gotten when the disintegration times of ciprofloxacin and metronidazole tablets in 0.1 N HCl solution were compared with the times obtained in AL tablet dispersed medium, even though ciprofloxacin tablets achieved a decreased disintegration time in the AL dispersed medium (24 sec faster). The reduction in the disintegration time of the ciprofloxacin tablets may be the result of a quicker fluid penetration into the tablet due to the quick eroding of the film coating of the tablet afforded by the AL tablet dispersion medium.

These disintegration time test results, therefore, implies that the disintegration processes of different tablets may not be appreciably affected when they are administered together orally.

The *in vitro* dissolution studies described the effect on artemether and lumefantrine release from AL tablets in 0.1 N HCl solution as a dissolution medium and also when ciprofloxacin or metronidazole tablets are dispersed in the medium. Conversely, the study also described the effect on the release of ciprofloxacin or metronidazole from their tablet formulations in plain 0.1 N HCl solution and in AL tablet dispersed media. While all the tablets released up to 70% of their drug content within 40 min in 0.1 N HCl solution, hence meeting the British Pharmacopeia specification (BP, 2009). However, the AL tablet's release of lumefantrine was slower though reaching over 70% release within the time frame of the dissolution test. There was significant retardation in the release of artemether and lumefantrine from their tablet in the presence of ciprofloxacin and metronidazole. This retardation was more pronounced with metronidazole than with ciprofloxacin. Similar levels of drug release retardation for metronidazole have been previously reported (Awofisayo *et al.*, 2018). Metronidazole was also implicated in affect drug permeability from dihydroartemisinin-piperaquine antimalarial product across intestinal membranes (Awofisayo *et al.*, 2017). These drug release retardation observations were not confined to the metronidazole and ciprofloxacin tablets alone as the AL tablets had the same effect on the release of ciprofloxacin and metronidazole from their tablets. Though some studies involving combination therapy of these drugs have yielded results that even suggest their synergistic action (Aly *et al.*, 2014; Adeoye-Isijola *et al.*, 2019), the results from this study will suggest an interaction between these drugs resulting in delays in their dissolution and release from their tablet formulations. These changes in their drug release may be due to alteration in the gastric pH since most orally administered drugs dissolve in varying gastric pH. The presence of some drugs in the gastric medium can change the pH of the medium to become neutral or alkaline and this can alter the kinetic of other co-administered drugs in the medium (Palleria *et al.*, 2013).

The FTIR studies further corroborate the absence of any chemical interaction or complex formation between artemether/lumefantrine and either ciprofloxacin or metronidazole by the alignment in their spectral patterns. This points to the fact that the drug release retardations that may be witnessed with concomitant administrations of these tablets are not chemically mediated.

CONCLUSION

The result from this study clearly demonstrates or shows that a level of drug interaction exists between the tablet formulations of artemether-lumefantrine and ciprofloxacin or metronidazole when they are co-administered orally. Although, there was no significant change in the disintegration time of each drug when in the presence of the others, however, there were significant reductions in the release of artemether-lumefantrine in the presence of ciprofloxacin or metronidazole. Also, a more drug release retardation was seen between artemether-lumefantrine and metronidazole than with ciprofloxacin and these changes in drug release indicated an absorption interaction, possibly due to alteration in gastric pH.

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