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Assessment of Spectroscopic Interaction of Lamivudine/Metronidazole with Dihydroartemisinin – Piperaquine Antimalarial Tablet

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Authors' contributions

This work was carried out in collaboration between the authors. Authors SOA and PDO designed the study. Author FAI wrote the protocol and the first draft of the manuscript. Authors NAJ and CNI managed the literature searches. Author SOA performed the spectroscopic analysis and managed the experimental process. All authors read and approved the final manuscript.

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ABSTRACT

In vitro interactions between dihydroartemisinin (DHA) or piperaquine (PQ) components of antimalarial dihydroartemisinin-piperaquine (DP) with lamivudine/metronidazole were studied using Fourier transform infrared spectroscopy (FTIR). One milligram of either of lamivudine or metronidazole was mixed with 1 mg of crushed and powdered DP tablet and the admixture pelletized with 20 mg potassium bromide (KBr) powder. The pellets were scanned at 2 mm/s over wavenumber region of 4000 to 500 cm^{-1}. The bond vibrations of DHA and PQ were consistent with

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the reference literature values. Lamivudine shifted (C=O) bond stretching of DHA from 1735 to 1649 cm^{-1} and (O-H) stretching from 2926 to 2922 cm^{-1}. The endoperoxide bond vibration was shifted from 875 to 866 cm^{-1}. Lamivudine also shifted the characteristic aromatic (C-H) bending of PQ from 775 to 796 cm^{-1}. The aromatic and aliphatic (C-N) stretchings were shifted from 1367 to 1384 cm^{-1} and 1274 to 1278 cm^{-1}, respectively. Metronidazole shifted the (C=O) stretching of DHA from 1735 to 1643 cm^{-1} and lactone (C-O-O-C) stretching from 875 to 883 cm^{-1}. The (O-H) stretching was shifted from 2926 to 2935 cm^{-1}. Piperaquine aromatic (C-H) bending was shifted from 775 to 727 cm^{-1} while aromatic (C-Cl) stretching vibration from 1145 to 1143 cm^{-1}. The vibrational spectra shifts caused by lamivudine and metronidazole on the characteristic spectra vibration of DHA and PQ were adjudged insignificant. There was no *in vitro* interaction between lamivudine/metronidazole and the actives of DP tablet. The drugs may not pose any biopharmaceutical implications on co-administration with DP tablet.

Keywords: Dihydroartemisinin-piperaquine; lamivudine; metronidazole; FTIR; drug interaction.

1. INTRODUCTION

In many malarious area of the world, more especially sub-Saharan Africa, malaria is rated among the most frequent causes of morbidity and mortality among children [1]. In addition to the burden of malaria with respect to morbidity and mortality, the weight of the direct costs for treatment and prevention as well as indirect costs in terms of productivity loss (*e.g.*, labour and time) make the disease bear a heavy toll on community development in tropical and sub-tropical regions (*i.e.,* sub-Saharan Africa, Central and South America, the Caribbean island of the Hispaniola, the middle East, the Indian sub-continent and South-East Asia Oceanic). The geographical spread of malaria and parasitic resistance to wide range of malaria drugs make the battle against the disease a worthy cause [2,3].

In tropical region, metronidazole is a household drug and is widely used for intestinal upsets and more appropriately prescribed for hepatic and intestinal amoebiasis [4-6]. These diseases have geographical similarity with malaria and malaria drugs may be co-prescribed. Lamivudine prescribed as an antiretroviral drug (ARD) in human immunodeficiency viral infection / acquired immune deficiency syndrome (HIV/AIDS) may also be co-prescribed with malaria drugs. The co-administration of drugs that interact one with the other has been widely reported as a major cause of therapeutic failure [7,8].

Dihydroartemisinin – piperaquine (DP) has been assessed *in vitro* and in clinical trials for almost a decade and shown to be highly efficacious against both *Plasmodium falciparum* and *P. vivax* infections [9,10]. The co-administration of drugs leading to drug-drug interaction with DP has not been extensively evaluated as a potential cause of drug treatment failure. Drug treatment failures in malaria and clinical cases of parasitic resistance and recrudescence have been widely reported [11].

Fourier transform infrared (FTIR) spectroscopy of physical mixtures of active ingredients and the proposed excipients have revealed unexpected interactions that can negatively impact on bioavailability and performance of drugs. FTIR therefore is a useful tool in qualitatively accessing the molecular integrity of actives in binary or complex mixtures [12].

This study was aimed at accessing the FTIR spectral changes on dihydroartemisinin or piperaquine vibrational features in the presence of lamivudine or metronidazole.

2. EXPERIMENTAL

2.1 Materials and Chemicals

Axcin DP ® (a brand of DP) was purchased in Lagos, Nigeria from a registered drug outlet. Lamivudine and metronidazole tablets were similarly purchased in Lagos, Nigeria. Details of the employed drugs are presented in Table 1. All other reagents were obtained commercially as analytical grade.

2.2 Methods

2.2.1 Instrumentation/analytical procedure

Dihydroartemisinin-piperaquine tablets were crushed and powdered in a mortar. One

milligram of either of the investigated drugs (*i.e*. lamivudine or metronidazole) was mixed with 1 mg of powdered DP, thereafter mixed with 20 mg potassium bromide and pelletized. The different pellets were scanned in a FTIR spectrophotometer (FTIR 8400S, Schimadzu, Japan) at the speed of 2 mm/s over a wavenumber region of 4000 – 500 cm^{-1}.

2.2.2 Analysis of spectra

The observed spectrum for DP was compared with the literature reference spectrum for artemisinin and piperaquine [13] and the observed spectra for DP mixed with powdered lamivudine tablet or powdered metronidazole tablet were compared with the observed spectrum for DP alone. The presence of significant spectra difference indicative of molecular interaction was adjudged using essential FTIR (eFTIR) software [14].

3. RESULTS

The employed product of DP, lamivudine and metronidazole used in this study were within their respective shelf lives as indicated in Table 1. The simultaneous admixtures of the investigated drugs (i.e., lamivudine or metronidazole) with powdered DP tablets were pelletized and these produced spectra characteristics for bonds and functional group vibrations for PQ. This is presented in Table 2. Similarly, the effects of simultaneous admixture of powdered DP tablet with lamivudine or metronidazole gave spectra characteristics for bonds in DHA and are presented in Table 3. The spectrum for DP alone and those of the respective investigated drugs were observed for comparison with their respective admixtures with powdered DP tablet. The spectra comparison for lamivudine is presented in Fig. 1 while that for metronidazole is presented in Fig. 2.

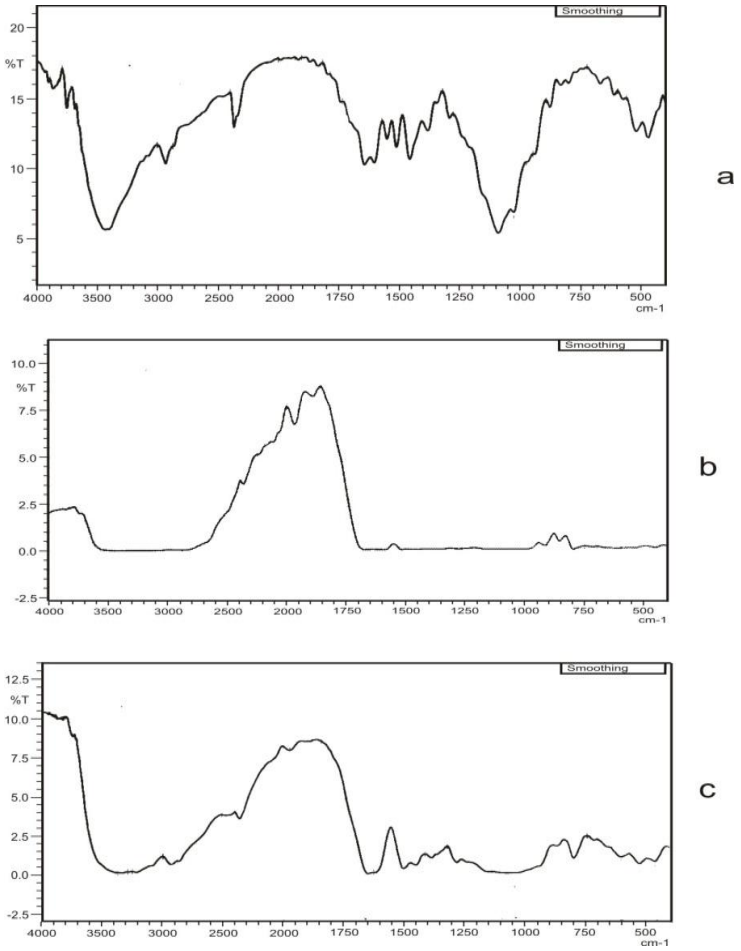

Fig. 1. Spectra of (a) powdered DP tablet, (b) powdered lamivudine tablet and (c) blend of powdered DP tablet and powdered lamivudine tablet co-pelletized

Table 1. Details of drugs used in the study

Drugs	Trade name	Source	Batch number	Registration number	Manufacturer
Dihydroartemisinin-Piperaquine	Axcin DP®	China		Yes	Vixa Chemical
Lamivudine	LEX ®	India	LEX-023	Yes	McNeil and Argus, India
Metronidazole	Loxagyl®	Nigeria	A150221	Yes	May and Baker, Nigeria

Table 2. Spectra shift of DHA vibrational band due to lamivudine and metronidazole

Functional group	Wavenumber (cm^{-1})		
	Lamivudine	Metronidazole	DHA
C=O stretching	1649	1643	1735
C-O-O-C stretching	866	883	875
C-H stretching	3331	3377	3419
O-H stretching	2922	2935	2926

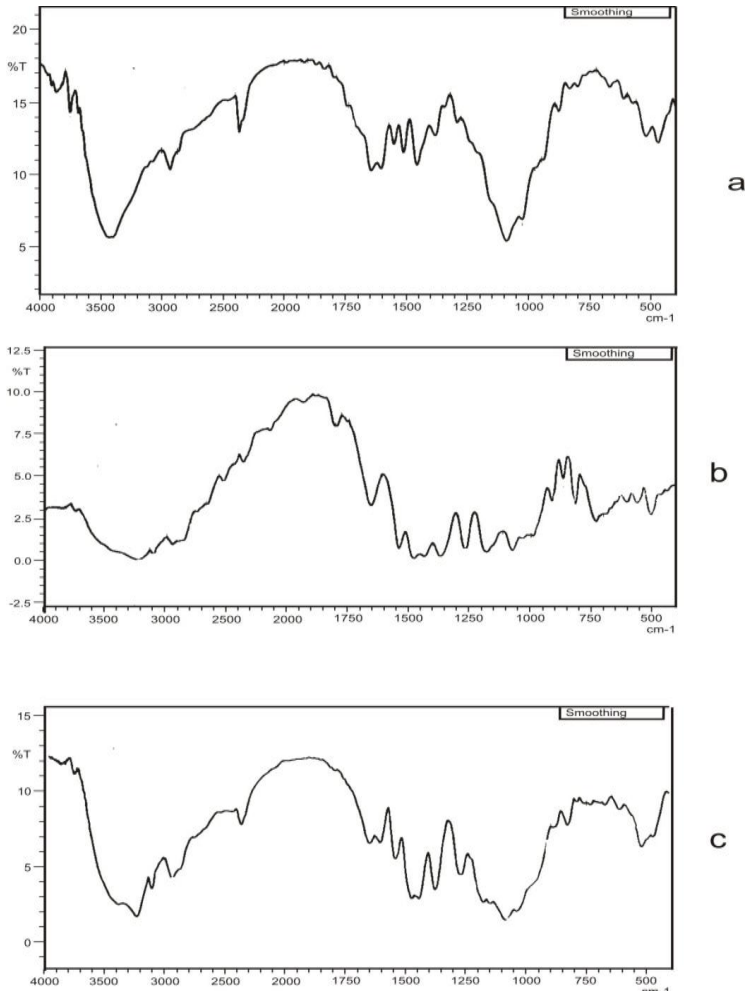

Fig. 2. Spectra of (a) powdered DP tablet, (b) powdered metronidazole tablet and (c) blend of powdered DP tablet and powdered metronidazole tablet co-pelletized

Table 3. Spectra shift of piperaquine vibrational band due to lamivudine and metronidazole

Functional group	Wavenumber (cm^{-1})		
	Lamivudine	Metronidazole	Piperaquine
Aromatic C-H bending	796	727	775
Aromatic C-H stretching	2922	3099	3009
Aliphatic C-H stretching	2864	2935	2874
Aromatic C-N	1384	1373	1367
Aliphatic C-N stretching	1278	1263	1274
Aromatic C-Cl stretching	1076	1143	1145

4. DISCUSSION

First, the infra red (IR) spectra of the powdered DP were compared with that of pure reference dihydroartemisinin and piperaquine obtained from the literature [13]. This was to ascertain that the bond vibrations that are characteristic of the actives in the selected DP drug product are intact and no interaction occurred between the actives or their accompanying excipients. This therefore can form the backdrop from which the possible interactions due to lamivudine or metronidazole can be premised.

This study revealed that the (C-H), (O-H) and (C-O) bonds that typify artemisinin molecules were present in the sample. The characteristic broad band of the (O-H) bond vibration due to dihydroartemisinin occurred at wavenumber 2926 cm^{-1} and that of (C-O-O) at the fingerprint region, 875 cm^{-1} (Table 2). These values were consistent with the literature data for dihydroartemisinin aforementioned bond vibrations [13]. Similarly, the characteristic bond vibrations for piperaquine were conspicuously featured for (C-Cl), aromatic (C-N) stretching and aromatic (C-H) bending vibrations which are consistent with the literature values. Reference dihydroartemisinin and piperaquine spectra features in the literature have confirmed the identity of the co-formulated actives in the DP product employed for this investigation [13]. Furthermore, the non-interaction of the excipients or the actives one with the other has been established as the eFTIR software adjudges the spectra obtained for DP cum potassium bromide pellets as possessing no significant difference from the reference spectra. This therefore forms a basis for this *in-vitro* drug - drug interaction investigation of DP with lamivudine or metronidazole.

Previous studies on artemisinin – based products established the co-formulation status of artemisinin derivatives with the partner products by highlighting these specific IR spectral vibrations [15,16].

In this study, Fig. 1a shows the spectral features of dihydroartemisinin and piperaquine co-formulated, while 1b and 1c the spectral expression of lamivudine and the co-pelletized dihydroartemisinin-piperaquine with lamivudine, respectively. The characteristic spectral features attributable to dihydroartemisinin as observed in its reference spectra were (C-O), (C-H) and (C-O-O) bond stretching and vibrations that occurred at wavenumber 1735, 3419 and 875 cm^{-1}, respectively. The effect of co-pelletization of lamivudine resulted in the shift of these peaks to 1649, 3331 and 866 cm^{-1}, respectively. The software adjudged that the respective changes in the spectra features of DHA in DP tablet were not significant and therefore no molecular interaction with DHA (Fig. 1 and Table 2). Similarly the effect of lamivudine on the spectra presentation of piperaquine in the DP tablet was adjudged to be insignificant.

Metronidazole when co-pelletized with DP produced a shift in the bond spectra features as presented in Table 3. The characteristic aromatic (C-H) bending vibration due to piperaquine at 775 cm^{-1} featured at 727 cm^{-1} when co-pelletized with metronidazole while that of its stretching was at 3009 but shifted to 3099. The large difference in the aromatic (C-H) stretching shift was noted. The region of wavenumber between 3000 and 4000 cm^{-1} has been only of supportive information as it often features broad bands that are not definitive [17,18]. The software adjudged that co-pelletization of metronidazole with DP tablet has not resulted in significant change in the spectra presentation of piperaquine. Similarly, dihydroartemisinin spectra features were shifted by the co-pelletization of metronidazole with powdered DP tablet. The observed (C-O) stretching for dihydroartemisinin

at 1735 cm^{-1} was shifted to 1643 cm^{-1} while the (C-O-O-C) functional group moved from 875 to 883 cm^{-1} (Table 3 and Fig. 2). The software analysis of the vibrational data for dihydroartemisinin adjudged that there was no significant difference due to the co-pelletized metronidazole.

5. CONCLUSION

This *in vitro* study revealed that there was no significant shift or deletion of the characteristic bond features of dihydroartemisinin or piperaquine by the investigated drugs (*i.e.*, lamivudine or metronidazole). There was therefore no interaction between lamivudine and metronidazole with the actives in DP tablet.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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