Journal of Pharmaceutical Research International

18(1): 1-13, 2017; Article no.JPRI.28516
Previously known as British Journal of Pharmaceutical Research
ISSN: 2231-2919, NLM ID: 101631759

In-vitro Studies of Food Interaction with Dihydroartemisinin – Piperaquine Antimalarial Tablet

Sunday O. Awofisayo[1*], Chioma N. Igwe[1], Nkechinyerem A. Jonathan[2], Alphonsus I. Francis[1] and Peter D. Ojobor[3]

[1]Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Uyo, Nigeria.
[2]Department of Clinical Pharmacy and Pharmacy Management, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria.
[3]Central Research Laboratory, University of Lagos, Lagos, Nigeria.

Authors' contributions

This work was performed in collaboration among the authors. Authors SOA and PDO designed the work, managed the literature search and wrote up the work. Author CNI scrutinized the write up and approved the first draft. Authors AIF and NAJ managed the data. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2017/28516
Editor(s):
(1) Cheng Wang, Division of Neurotoxicology, National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), USA.
Reviewers:
(1) Alicia García Falgueras, The Official College of Psychologists, Madrid, Spain.
(2) Heethal Jaiprakash, MAHSA University, Malaysia.
(3) Norma Aurea Rangel Vazquez, Mexico.
(4) Sanjay Mishra, IFTM University, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/20364

Original Research Article

Received 22nd July 2016
Accepted 30th August 2016
Published 4th August 2017

ABSTRACT

The study assessed molecular interactions between the actives in antimalarial dihydroartemisinin-piperaquine (DP) tablet and food components using Fourier transform infrared spectroscopy (FTIR). Soluble starch, lactose, albumin, sunflower oil and carbonated drinks were pelletized with powdered DP tablet simultaneously using potassium bromide (KBr) method and analyzed with essential FTIR (eFTIR) software. Dihydroartemisinin (DHA) and piperaquine (PQ) showed characteristic bond vibrations consistent with reference to literature values. Carbohydrates food components had no significant effect on the DHA and PQ characteristic vibrations. Albumin powder shifted the aromatic (C-H) stretching of PQ from 3009 to 3387 cm^{-1}, and aliphatic (C-H) stretching at 2874 to 2935 cm^{-1}. DHA (C-H) stretching at 3419 cm^{-1} was shifted to 3387 cm^{-1} on admixture

**Corresponding author: E-mail: jdjide@gmail.com, jdjide@yahoo.com;*

with albumin without significant shift for endoperoxide link (*i.e*., 875 to 881 cm^{-1}), (C=O) stretching (*i.e*.,1735 to 1743 cm^{-1}) and (O-H) stretching (2926 to 2928 cm^{-1}). Sunflower oil caused a shift of the DHA spectra feature for (C-H) stretching at 3419 to 3385 cm^{-1}. Sunflower oil also shifted the aromatic (C-H) bending for PQ from 775 to 721 cm^{-1}. Carbonated drink admixture with DP tablet significantly shifted all the spectra features of PQ and DHA. Albumin and carbonated drinks produced significant changes in the spectra features of the actives in DP. Ingestion of protein meals or carbonated drinks with DP tablet may affect the bioavailability of the actives.

Keywords: Dihydroartemisinin-piperaquine; food components; carbonated drinks; FTIR.

1. INTRODUCTION

Dihydroartemisinin (DHA) and piperaquine (PQ) are employed for their synergistic effect and co-formulated to give a fixed-dose combination (FDC) antimalarial product [1]. The combination has a rapid plasma schizonticidal activity with effective symptom control for multi-drug resistant *falciparum* malaria. The co-formulated drugs have been reported to possess remarkable inhibitory effect on *falciparum* gametocyte thereby minimizing malaria transmissibility [2].

Oral administration of dihydroartemisinin-piperaquine (DP) leads to rapid absorption of the component drugs in the gastrointestinal (GI) tract, giving better drug exposure, *in vivo* [2]. PQ is well absorbed and detectable in plasma after 0.5 h post dosing, reaching peak concentration in 1 – 2 h. DHA like other artemisinin derivatives has rapid effect but short half life [3]. Artemether has been reported to be metabolized to DHA *in vivo* and the later possessing higher antimalarial activity than the parent drug [4]. The intrinsic stability problem of DHA was a subject of controversy with respect to drug development [4]. Products of DHA were reported to pass chemical content test during quality assurance testing but failed after drug release to the market [4]. It will be necessary to further follow up on the performance of DP antimalarial formulation to its bioavailability positions as different meal types are known to be ingested with orally administered antimalarial drugs. The effect of food may cause variations and complicate predictability of blood levels of orally administered drugs, thereby influencing their therapeutic outcome.

Furthermore, resistance to antimalarial agents is a topical issue. The rapidly emerging parasitic resistance to most developed conventional and co-formulated artemisinin combination drugs has meant that factors responsible for the undue orchestration of parasitic resistance be evaluated [5].

Drug-food interactions have been documented when a drug of interest is taken with food leading to variability in drugs pharmacokinetic profile of either drug [6]. Ingested food can alter the dissolution, stability and bioavailability of the analyzed drugs, thus affecting its safety and efficacy [7-9].

Analytical techniques such as Fourier transform Infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and scanning electron microscope (SEM) are instrumental approaches to characterize the status of drug of interest as to make preliminary decisions on overall outcome of food interaction with drugs [8].

This study seeks to evaluate *in vitro* interaction of DP tablet with food components by comparing FTIR spectra features of admixtures.

2. EXPERIMENTAL

2.1 Materials and Chemicals

Dihydroartemisinin-piperaquine, Axcin DP®, product of Vixa chemicals was purchased in Uyo, Southern Nigeria from a registered drug outlet. The food components employed were bought in Lagos, Nigeria and details presented in Table 1. All reagents used were of analytical grade.

2.2 Methods

2.2.1 Instrumentation/analytical procedure

The (infra-red) IR studies were performed using spectrophotometer 8400S (Schimadzu, Japan) Potassium bromide disc method was employed. The DP tablet was crushed to powder. One milligram of the DP was mixed with 200 mg of

Table 1. Details of food components employed in the study

Name of food component	Manufacturing date	Expiry date	Batch number	Origin
Albumin	01-2014	12-2016	Alpha Chemika	India
Glucose	05-2013	12-2016	Quigyuang Ltd.	China
Lactose	03-2014	02-2016	Triveni chemicals	China
Fructose	08-2013	07-2017	Park services	Ukraine
Starch	05-2013	05-2017	Park services	Ukraine
Sunflower oil	01 2012	01-2017	JiannHairu Co.	China
Vitamin A	02-2014	03-2017	Private label Ltd.	USA
Carbonated drink	05-2014	11-2015	Coca-cola Company	Nigeria

dried potassium bromide powder and compressed to form pellet in a translucent disc. The scanning was performed at a speed of 2 mms^{-1} over a wavenumber region of 4000 to 500 cm^{-1}.

2.2.2 Analysis of spectrum

The observed spectrum for DP was compared with reference spectrum in the literature for artemisinin and PQ (WHO, 1999) and the observed spectra for DP mixed with food components were compared with the observed spectrum for DP alone and significant difference indicative of molecular interaction was adjudged using essential FTIR (eFTIR) software.

3. RESULTS

The employed product of DP used in this study was the most widely prescribed generic in the area. All the food components employed were within their shelf lives. The simultaneous admixture of each food component with powdered DP tablets and thereafter pelletized, produced spectra characteristics for bonds and functional group vibrations of PQ and DHA that are presented in Table 2 and Table 3, respectively.. Similarly, the effects of admixture with food components and the spectra characteristics for bonds in DHA are presented in Table 3. The spectrum for DP alone, the respective food components assessed and that of the admixture are presented in Figs. 1-7.

4. DISCUSSION

In this study, the basic food components (*i.e*., carbohydrate, protein, fat/oil and vitamin) and carbonated drinks were investigated for their influence on the spectral features of DHA and PQ by spectroscopic assessment. The presence of molecular interaction between the actives of DP was assessed employing the techniques of FTIR spectroscopy. This study analyzes the stretching vibrations (*i.e*., indicative of the change in the distance between atoms) or the bending vibrations of functional groups (*i.e*., carboxyl, carbonyl, hydroxyl or amino) bonds comparing the theoretical and the observed spectrum. It was observed that the characteristic bands exhibited by the DP sample (*i.e*., Axcin DP®) featured the vibrational bands for both DHA and PQ. The spectral features of DP showed that the actives were co-formulated and there were no interaction with the employed excipients in the complex blend. This confirmed the co-formulation status of the two compounds in the antimalarial product [10,11]. Similar study by Lawal and co-workers on the spectroscopic evaluation of artemisinin and its derivatives using pure samples of artesunate and artemisinin reported that the vibrational data of their samples were in conformity with that of the literature [12].

In the reference spectra for DHA and PQ, the high wavenumber region (*i.e*., within 4000 to 3000 cm^{-1}) featured stretching vibrations that correspond to aromatic (C-H) stretching at 3009 cm^{-1} due to PQ and aliphatic (C-H) due to DHA at 3419.79 cm^{-1}. Mid wavenumber region featured aliphatic (C-H) stretching at 2874 cm^{-1}, aromatic amino (C-N) stretching at 1367 cm^{-1} and aliphatic amino (C-N) stretching at 1274 cm^{-1}, characteristic peaks of piperaquine infrared vibration assignment. The stated values were analyzed as the baseline for PQ characteristic spectra band. This study revealed that the different food components shifted the spectral features for piperaquine to different extent. Carbohydrate food components (*i.e.,* fructose, glucose and lactose) were pelletized with DP in turns and their effects on DP spectra features observed. Their effects were adjudged to be insignificant therefore no molecular interaction existed with DP (Figs. 1-3). The extensive hydroxyl groups on the carbon skeleton are

expected to form a platform for H-bonding with the piperaquine nitrogen atom lone pair electrons. Table 1 gives the respective vibrational spectra for PQ when co-pelletized with the different food components and carbonated drinks.

Carbohydrate sugars have available active sites for interaction. The hydroxyl groups on sugar chemical structures appear to be the only available active points for any chemical or molecular interaction with other molecules. However, sugars have been reported to be low in reactivity. In the study area, sugars form a higher proportion of meals. As meal times are connected with dosing conditions, the reactivity of drugs with food may explain the reasons for the variable drug levels in dosing conditions [13].

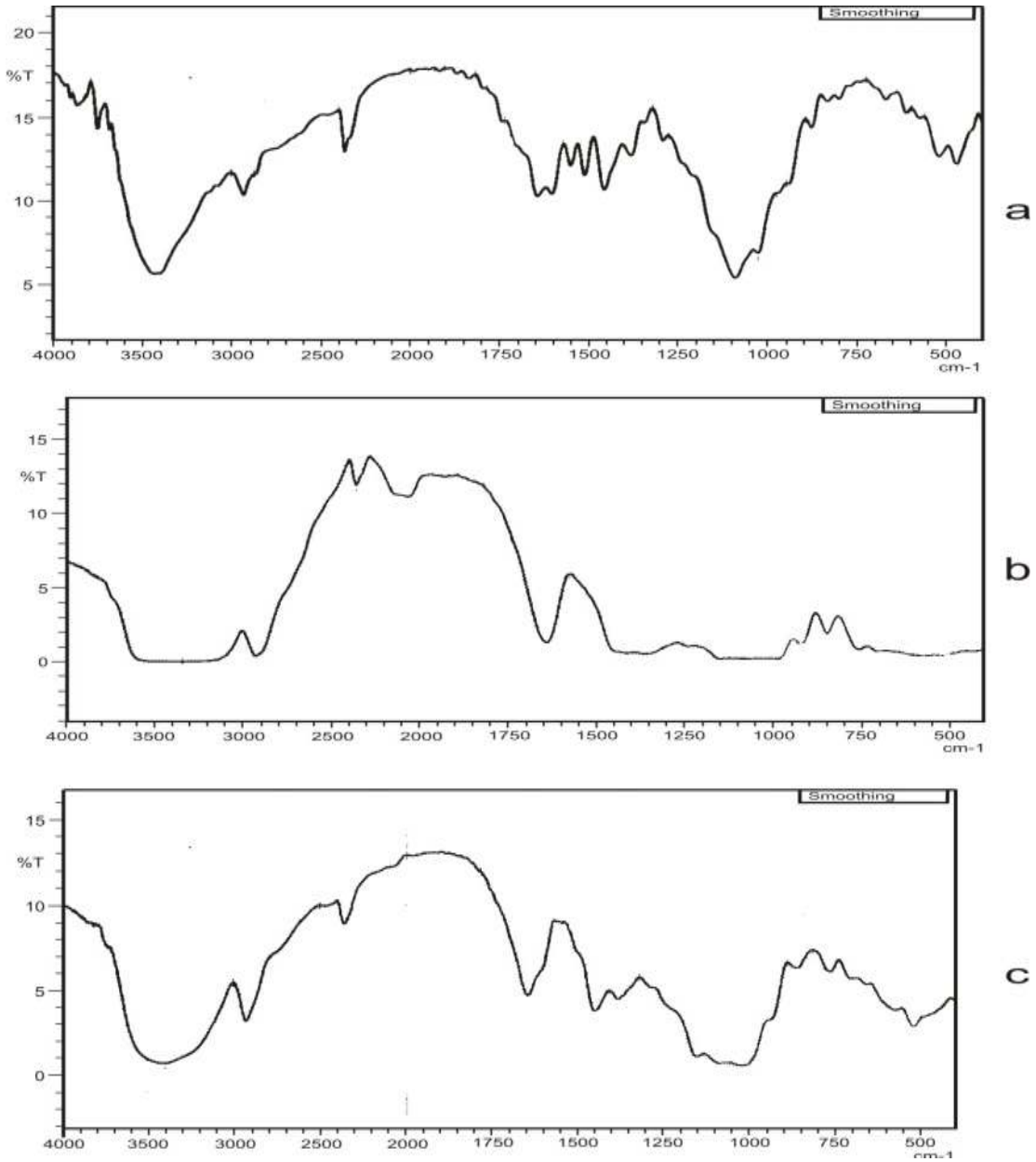

Fig. 1. Spectra of (a) Powdered DP tablet, (b) Starch powder and (c) Blend of powdered DP tablet and starch powder co-pelletized

Table 2. Spectra shift of PQ vibrational band due to food components

Functional group	Wavenumber (cm^{-1})							
	Starch	Fructose	Lactose	*S. oil	Albumin	Vitamin A	Coca-cola®	Piperaquine**
Aromatic C-H bending	765	777	767	721	813	769	669	775
Aromatic C-H stretching	2929	3514	3381	2926	3387	3402	3562	3009
Aliphatic C-H stretching	2929	2937	2937	2858	2935	2929	2320	2874
Aromatic C-N	1379	1344	1344	1379	1386	1381	1460	1367
Aliphatic C-N stretching	1379	1244	1244	1159	1232	1234	1060	1274
Aromatic C-Cl stretching	1153	979	1078	1159	1232	1145	1460	1148

*NB: * S. oil means sunflower oil. **The reference piperaquine wavenumber for the respective functional group vibration. Wavenumber values were taken to the nearest whole number*

Table 3. Spectra shift of DHA vibrational band due to food components

Functional group	Wavenumber (cm^{-1})							
	Starch	Fructose	Lactose	*S. oil	Albumin	Vitamin A	Coca-cola®	**DHA
C=O stretching	1643	1651	1651	1743	1651	1737	1645	1735
C-O-O-C stretching	860	881	885	881	881	862	669	875
C-H stretching	3398	3387	3381	3385	3387	3402	3562	3419
O-H stretching	2929	2935	2912	2928	2935	2929	2320	2926

*NB: * S. oil means sunflower oil. **The reference dihydroartemisinin wavenumber for the respective functional group vibration. Wavenumber values were taken to the nearest whole number*

Proteins form a low proportion of meals in resource-limited countries. Co-pelletization of albumin with DP produced dramatic shift in the peak attributed to aromatic C-H stretching on PQ located at 3009 to 3387 cm^{-1} (corresponding to a displacement of 378 cm-1). This is due to extensive influence of H-boding occurring between albumin and PQ. Similarly, the peak that featured at 2874 cm^{-1} was shifted to 2964 cm^{-1} (corresponding to a shift of 90 cm^{-1}). Hydrogen bonds are formed by interactions between amino group and electronegative oxygen (*i.e*., N-H…O) or hydroxyl group with proximal electronegative nitrogen (*i.e*., O-H…. N). The presence of H-bonds between samples containing hydroxyl, amino and carboxyl groups changes the baseline stretching vibrations as observed in the spectral changes depicted in Fig. 4 [14,15]. Berg et al. reported on the mechanism of molecular interaction involving H-boding in the presence of the hydrogen acceptor, hydrogen and the hydrogen donor. In the study, the FTIR theoretical spectrum and the observed spectrum for the mixture indicated that there was an interaction between the molecules.

IR spectra due to DHA at 3419 shifted to 3387 cm^{-1} with an intensity of 6.67 in the new blend involving albumin powder and powdered DP tablet (Fig. 4). Similarly, spectra vibration of (C-H) stretching for DHA at 2926 shifted to 2935 cm^{-1}, a wavenumber difference of 9 cm^{-1} and intensity of 11.53. The spectra features at 1917 and 1838 cm^{-1} were deleted due to the presence of albumin (Table 2). Proteins are composed of amino acids with carboxylic and amino groups that can promote interaction with drugs carrying complementary reactive centres. The functional groups in amino acids also facilitate extensive H-bonding that can lead to formation of molecular bonds. The employed software confirmed that there was significant change in the baseline spectra of DP occasioned by the presence of albumin powder, hence a molecular interaction existed.

Sunflower oil caused a shift of the DP spectra feature at 3419 to 3385 cm^{-1}. This shift of 34 cm^{-1} and intensity of 6.54 indicated an association between sunflower oil and the actives of DP tablet. Previous studies have reported that fatty foods or oils increased the bioavailability artemisinin based drugs, more so, the partner drugs in artemisinin combined therapy [16]. The shift observed therefore can be attributed to solvation characteristics of the oil on the actives of the antimalarial product [17-19]. Since there were no differences in the other spectra features of DP (*i.e*., peak at 2926 cm^{-1} due aliphatic C-H bonds for piperaquine and (O-H) bonds for DHA), it suffice to note that there was no molecular interaction between sunflower oil and the actives in DP tablet. The employed software adjudged that there was no significant difference in the effect of sunflower oil on the vibrational spectra of the actives in DP tablet.

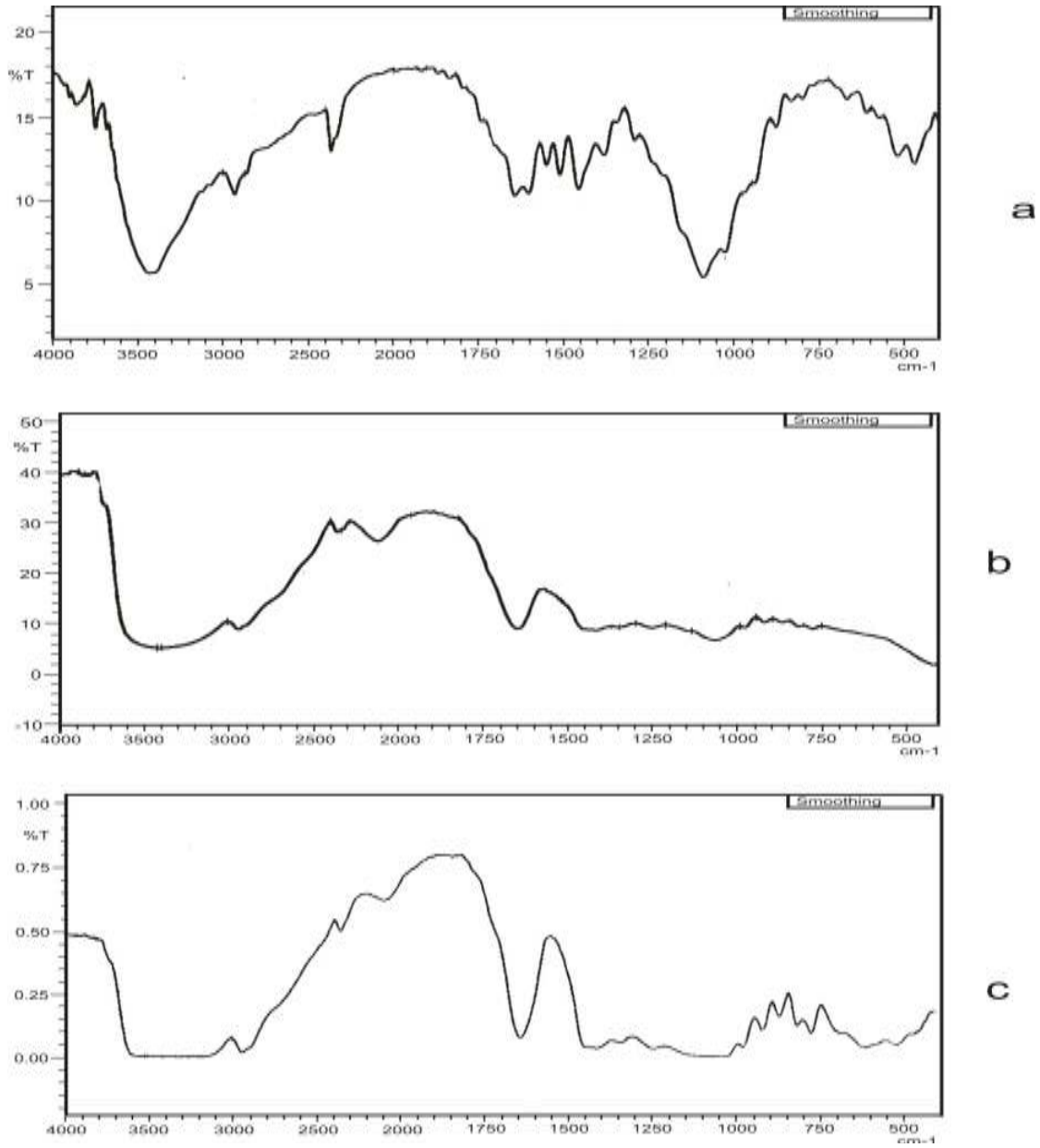

Fig. 2. Spectra of (a) Powdered DP tablet, (b) Fructose powder and (c) Blend of powdered DP tablet and fructose powder co-pelletized

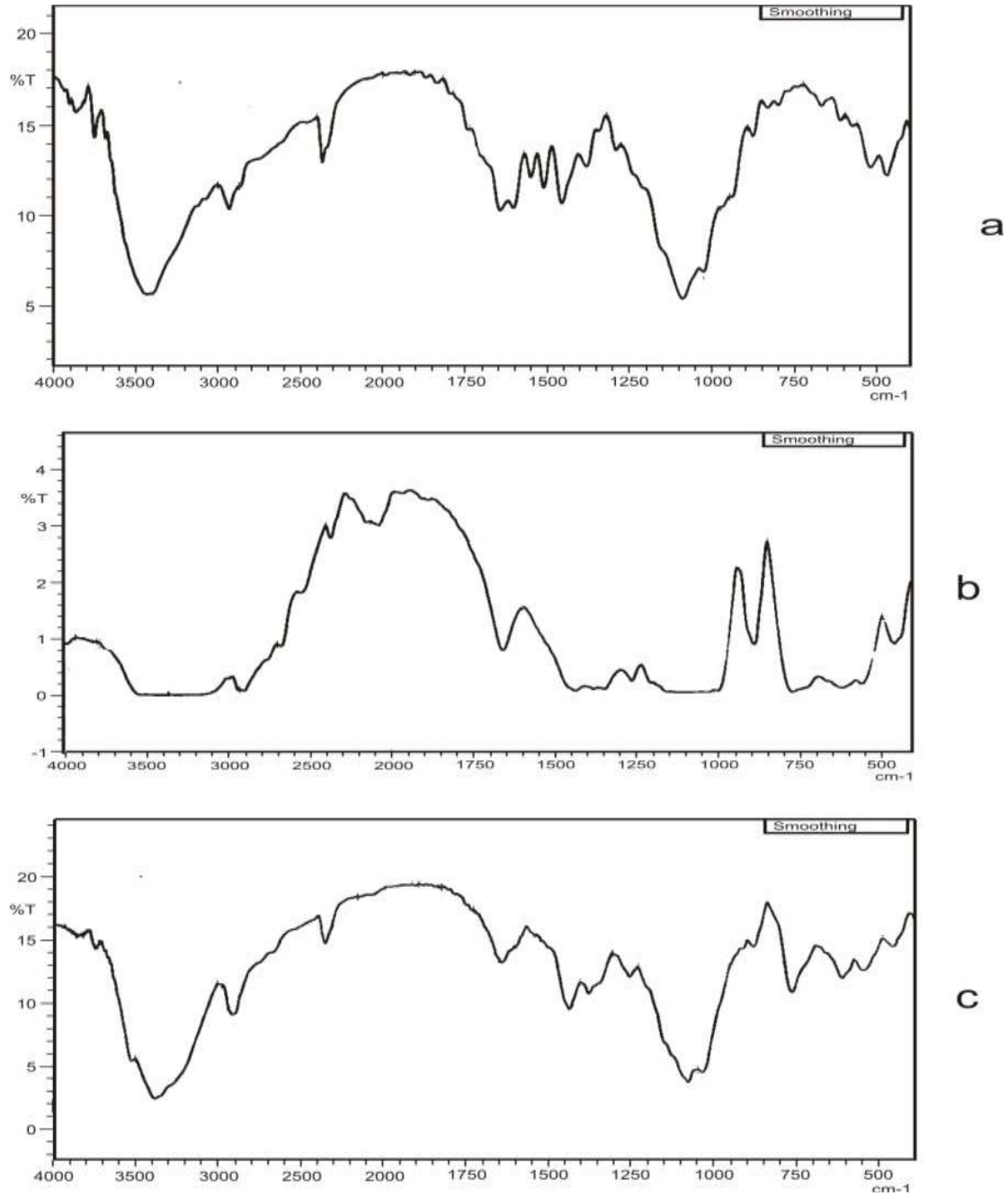

Fig. 3. Spectra of (a) Powdered DP tablet, (b) Lactose powder and (c) Blend of powdered DP tablet and lactose powder co pelletized

Cocacola® and Fanta® are commonly relished carbonated drinks in the study area, hence included in this study. The drinks are common feature on tables during meals and are sometimes used to ingest medication. Fig. 7 presented the spectra of DP when co-pelletized with the carbonated drinks. The employed software adjudged the carbonated drink to have molecular interaction with the actives in DP tablet. Comparing the baseline vibrational spectra with the spectra for co-pelletized DP tablet with carbonated drinks, it was evident that the functional group characteristics (*i.e*., for DHA and PQ) were significantly shifted.

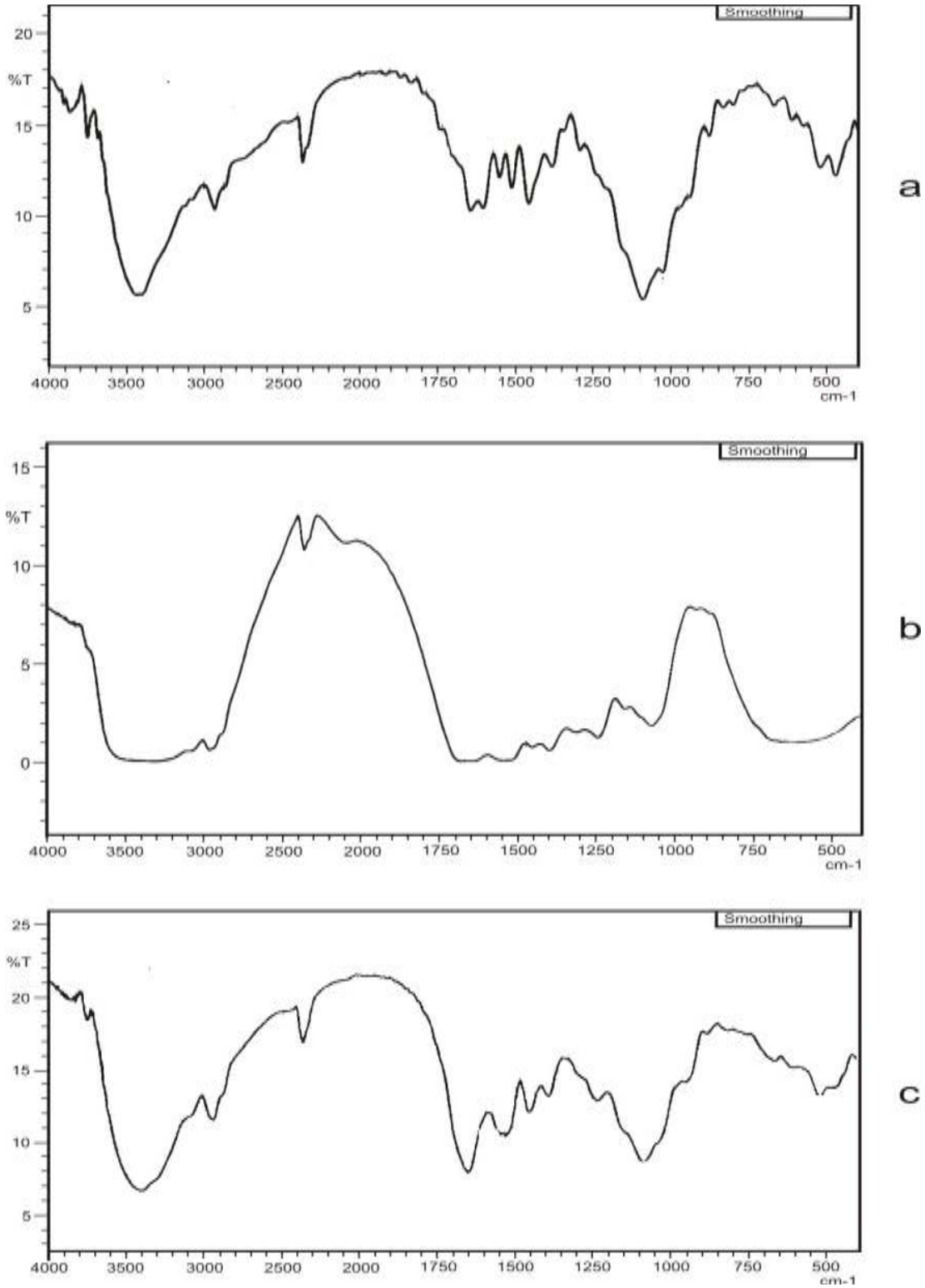

Fig. 4. Spectra of (a) Powdered DP tablet, (b) Albumin powder and (c) Blend of powdered DP tablet and albumin powder co-pelletized

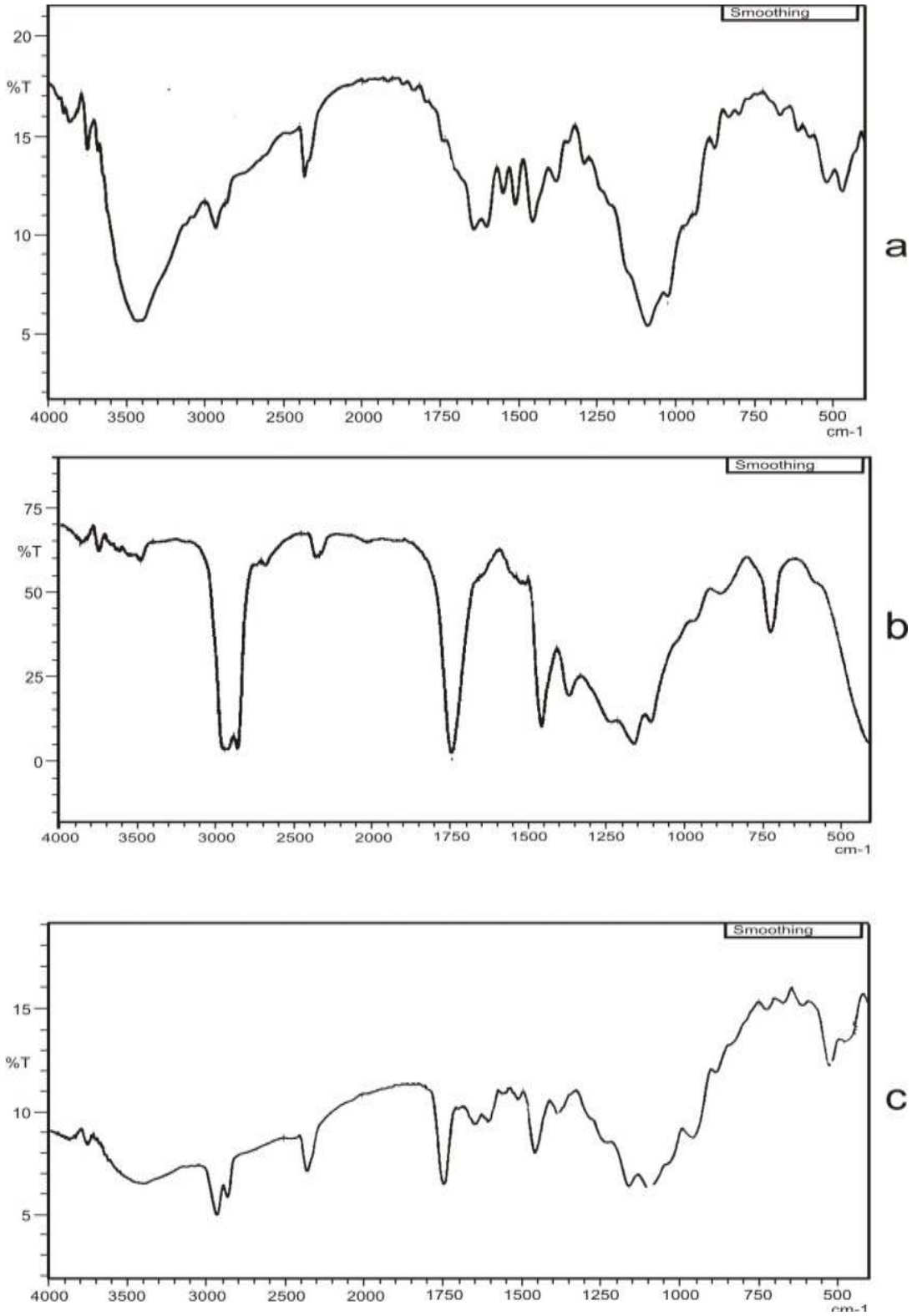

Fig. 5. Spectra of (a) Powdered DP tablet, (b) Sunflower oil and (c) Blend of powdered DP tablet and sunflower oil co-pelletized

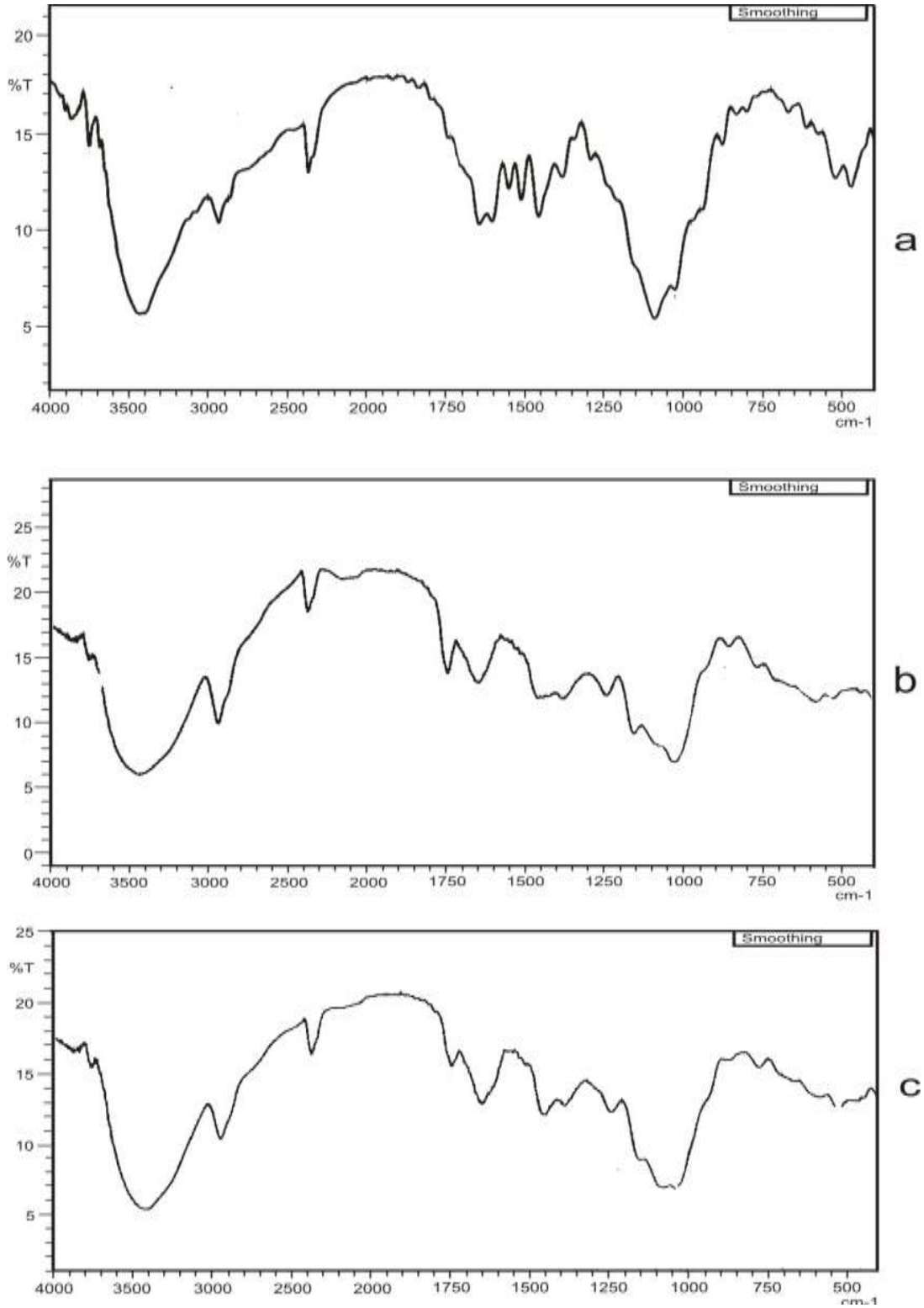

Fig. 6. Spectra of (a) Powdered DP tablet, (b) Vitamin A powder and (c) Blend of powdered DP tablet and vitamin A powder

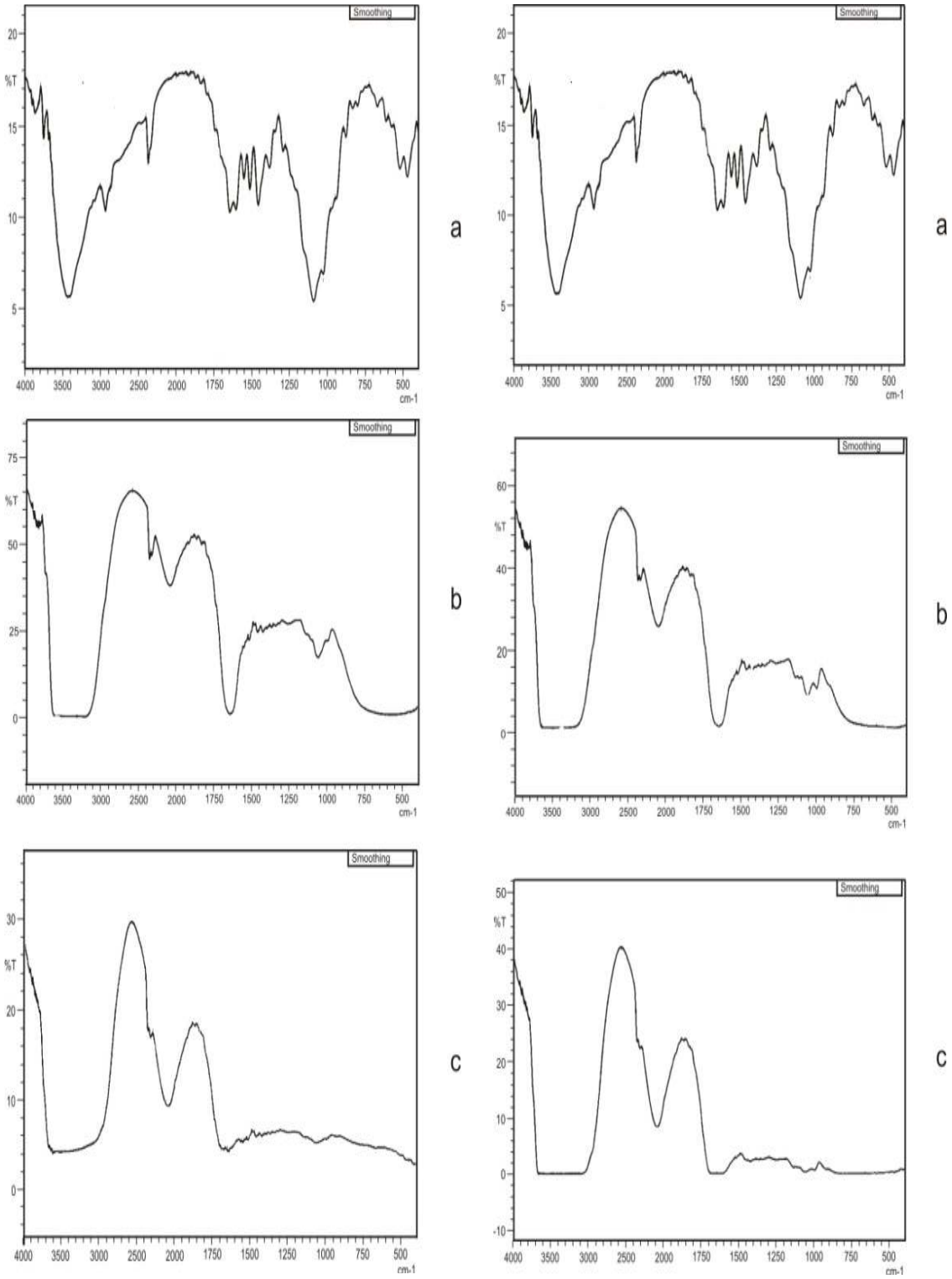

Fig. 7. Spectra of (a) Powdered DP tablet, (b) Carbonated drink Cocacola® and Fanta®, on left and right, respectively and (c) Blend of powdered DP tablet with the respective carbonated drinks

5. CONCLUSION

In conclusion, molecular interactions of DP with food components were observed in FTIR spectra. Albumin was adjudged to cause significant spectra band shift and therefore possessing chemical interaction with both DHA and PQ components of DP tablet. Similarly, carbonated drinks (*i.e*., Cocacola® and Fanta®) also presented significant spectra changes indicative of chemical interaction with DP tablet. The dosing conditions involving food and drinks with DP tablet may affect the oral absorption of the actives in DP tablet in malaria treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nosten F, Brasseur P. Combination therapy for Malaria. Drugs. 2002;62:1315–29.
2. Densi MH, Davis TM, Hewilt S. Efficacy and Safety of Dihydroartemisinin – piperaquine (Artenin) in Cambodian Children and Adults with uncomplicated falciparum malaria. Clinical Infectious Diseases. 2002;35:469–76.
3. Van Boxtel CJ. Antimicrobial agents. In drug benefits and risks: International textbook of clinical pharmacology. Van Boxtel CJ, Santoso B, Edward IR (eds). John Wiley Publishers. 2001;334-335.
4. Finch RG. Malaria. In antibiotics and chemotherapy. Finch RG, Greenwood D, Whitley RJ, orbby SR (eds). Elsevier Health Sciences. 2010;813-817.
5. Hung NM, Hewilt, S. Davis TM. Resistance of *Plasmodium falciparum* to antimalarial drugs in a highly endemic area of Southern Vietnam: A study *in-vivo* and *in-vitro*. Transactions of the Royal Society for Tropical Medicine and Hygiene. 2001; 95:325–329.
6. Ansani JA. Drug interaction and pharmacists. Journal of Young Pharmacists. 2010;2(3):325-331.
7. Ayo JA, Agu H, Madaki I. Food and drug Interactions; its side effects. Nutrition and Food Science. 2005;35(4):243-252.
8. Bushra R, Nousheenn A, Arshad YK. Food-drug interaction. Omar Medical Journal. 2011;26(2):77-83.
9. Frankel EH. Basic concepts. In: Handbook of food-drug interactions. McCabe BJ, Frankel EH, Wolfe JJ (eds.). CRC Press, Boca Raton. 2003;2.
10. World Health Organization. WHO expert committee on specification for pharmaceutical preparations, thirty-fifth report-technical report series. Reference Substances and Infrared Reference Spectra for Pharmacopoeia Analysis (WHO Technical Report Series No. 885, 1999: Annex 3).
11. The International Pharmacopoeia 3rd ed. Vol 1, General methods of analysis; Vol 2 Quality specifications; Vol 3 Quality specifications; Vol 4. Tests, methods and general requirements. Quality Specifications for pharmaceutical substances, excipients and dosage forms, Geneva, World Health Organization, 1979-1994.
12. Lawal A, Umar RA, Abubakar MA, Faruk UZ, Wali U. FTIR and UV-visible spectrophotometric analysis of artemisinin and its derivatives. Journal of Pharmaceutical and Biomedical Sciences, 2012;24(4):6-14.
13. Segal EM, Flood MR, Maciani RS, Whiteman RT, Friedt GA, Kramer AR, Hofsletter MA. Oral chemotherapy food and drug interaction: A comprehensive review of the literature. Journal of Oncology Practice. 2014;10(4):e255-61.
14. Berg JM. Chemical Bonds in Biochemistry. In Biochemistry. Berg JM, Tymoczko JL, Styrer L (eds.) 5th Ed. Freeman and Company, New York. 2002;35-40.
15. Stiner T. The hydrogen bond in the solid state. Angewandie Clinic International Edition. 2002;41:49–76.
16. Kanshal AM, Chakroborti AK. Bansal AK. FTIR studies or differential intermolecular association in crystalline and amorphous states of structurally related non-steroidal anti-inflammatory drugs. Molecular Pharmaceutics. 2008;5:937-45.

17. Premji ZG, Abdulla S, Ogutu B, Ndong A, Falade CO, Sagara I. The content of African diet adequate to achieve optimal efficacy with fixed dose artemether-lumefantrine; a review of the evidence. Malaria Journal. 2008;7:244-49.
18. Sanders JKM, Hunter CA. The nature of *pi-pi* Interactions. Journal of the American Chemical Society. 1990;112: SS25–SS34.
19. Hemley R, Kohler B. E, Siviski P. Absorption spectra for the complexes formed from vitamin A and beta-lacto globulin. Biophysical Journal. 1979; 28:447–455.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20364