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Non-thermal and thermal compatibility studies of binary blends of amlodipine and common spices; clove, ginger and turmeric

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ABSTRACT: A lot of people on anti-hypertensives including amlodipine often take their medications with their tea or beverages. Many are conscious of the health benefits of medicinal plants and prefer going with green or common spices like clove, cinnamon, turmeric, ginger, garlic, etc. In spite of that, the compatibility or otherwise of consumption of these spices simultaneously with amlodipine is questionable. The aim of this study is to assess the solid-state compatibility of amlodipine with some selected spices: clove, ginger, turmeric using Fourier Transform InfraRed (FT-IR) and Differential Scanning Calorimetry (DSC). FT-IR spectra show that the combination of amlodipine with the spices brought about some shifts in wavenumbers, reduction in intensity, broadening to varying degrees but no significant chemical interactions were detected. On the other hand, DSC analysis showed disappearance of amlodipine peak in the drug-spice combination with some changes in the temperature of different events. This suggests that the combination of amlodipine with the spices could compromise its thermal stability. It is therefore inferred that whereas many people enjoy taking their medications along with these beverages or spices, this combination proves to be unsuitable especially in the light of formulation as a combination product.

KEYWORDS: Amlodipine; Clove; Ginger; Turmeric; Fourier Transform InfraRed; Differential Scanning Calorimetry.

1. INTRODUCTION

Medicine has progressed over the years and in recent times with the re-introduction of herbal medicine in health care delivery. The use of plant remedies in managing or treating diseases has been well documented and is becoming a secondary source of medical care in some parts of the world [1]. In particular, consumption of teas or spices obtained from leaves, roots, barks and seeds of plants have been documented as beneficial for treatment for many diseases [2]. Many people consume herbal remedies along with the conventional medicines without recourse to the effect of this co-administration because of the purported belief that herbal medicines are safe. However, several drug-herb supplement/remedy interactions have been reported in literature which implies caution in their consumption especially in conjunction with other medicines [3].

Hypertension is one of the world's leading causes of death and disability and is therefore an important public health problem. About 1.28 million adults have hypertension with two-third of them living in developing countries like Nigeria [4]. Medical professions prescribe some drug regimen to effectively control hypertension. However, some people resort to the use of alternative medicines such as herbal remedies to manage this condition. Amlodipine is a calcium channel blocker which can be used alone or in combination with other medicines to lower blood pressure. It is common knowledge that people take this drug (as with other drugs) with teas, brews or beverages instead of with water which may not have the intended benefit but could be detrimental.

Studies in literature reveal different degrees of interaction between conventional antihypertensives with focus on amlodipine and herbal remedies like brews, teas or extracts. The study by Vaneková [5]

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reported elevated blood levels of amlodipine when combined with quercetin suggesting possible interaction between them. A different study reported that consumption of curcumin or turmeric with amlodipine does not bring about any synergistic effect in lowering blood pressure nor does it affect the blood-lowering effect of amlodipine [6]. The study by Alam [7] reported significant unhealthy blood pressure lowering effect of amlodipine when co-administered with zingiber officinale or hibiscus sabdariffa, in addition, another study revealed its co-administration with Lepidium sativum and curcuma longa enhanced the blood pressure lowering effect [8]. Cumin and green tea co-administered with amlodipine was observed to increase blood levels of amlodipine and prolong the half-life (t1/2) of amlodipine revealing a potential interaction between the drug and herbal remedies [9]. Some other study reported increased development of side effects including arthritis, elevated blood cholesterol upon co-administration of amlodipine and ginger.

Clinically, there are documentations that show potential interaction when amlodipine is consumed with herbal remedies. Nevertheless, many are still inclined to consume their medicines with green teas and or spices like clove, cinnamon, turmeric, ginger, garlic, e.t.c which they know have some health benefits. The question however, is how compatible or otherwise is the consumption of these spices simultaneously with administration of such drugs like amlodipine especially from a formulation point of view. Most ingredients that are included in formulation processes may not have any direct pharmacological action but they impact the feasibility of the formulation or stability of the product resulting in drug degradation which would bring about adverse drug reactions that would ultimately affect the therapeutic efficacy of the drug [10, 11]. These compatibilities can be monitored using non-thermal analytical techniques like Fourier Transform InfraRed (FT-IR) and thermal analytical techniques like Differential Scanning Calorimetry (DSC).

This study seeks to assess the solid-state compatibility of amlodipine with some selected spices (clove, ginger, turmeric) using Fourier Transform InfraRed (FT-IR) and Differential Scanning Calorimetry (DSC).

2. RESULTS

2.1. Fourier Transform InfraRed (FT-IR) studies

In this study, Fourier Transform InfraRed (FT-IR) spectroscopy analysis was done to investigate any physico-chemical incompatibility between the amlodipine and the spices (clove, ginger and turmeric). The results show the spectrum of amlodipine alone displayed in Figure 1 was characterized by a principal absorption band at 3295.0 cm^{-1} and a weak medium absorption band at 3157.1 cm^{-1}. Another characteristic band of small intensity peak was observed at 2981.9 cm^{-1}, strong absorption peaks at 1669.8 cm^{-1} and 1490.9 cm^{-1} and a medium intensity peak at 1263.6 cm^{-1} were also noted. Figure 1 also showed a weak intensity peak at lower absorption numbers around 752.9 cm^{-1}. Table 1 shows the comparison of reported peaks and those observed in this particular study and the functional groups of the corresponding peaks .

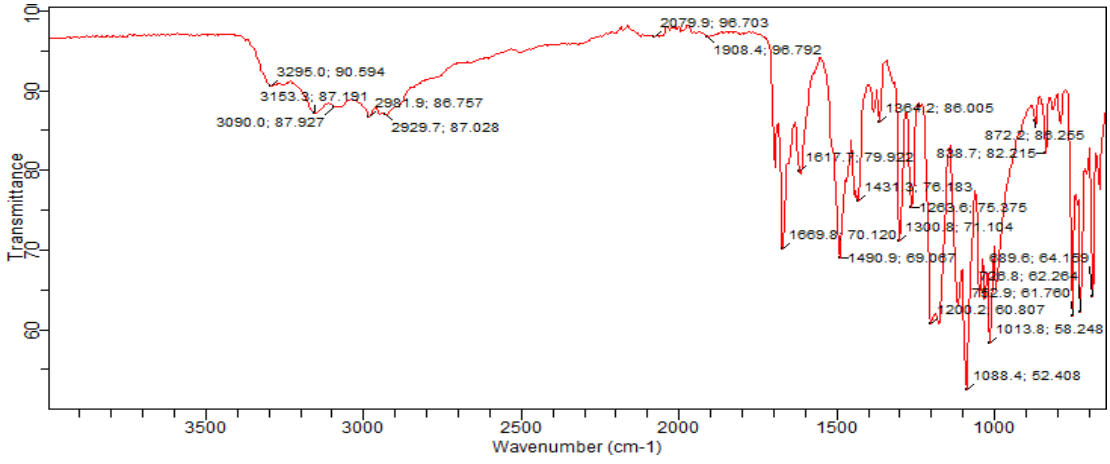


Figure 1. FTIR spectrum of pure amlodipine.

Table 1. Reported peaks of amlodipine compared to observed peaks of amlodipine in this investigation

Reported peaks (cm^{-1})	Observed peaks Amlodipine (cm^{-1})	Functional groups corresponding to peaks
3157.47	3153.3	-OH stretching of SO_3H
3298.28	3295.0	-N-H stretching of primary amino group
2985.52	2981.9	-C-H stretching of benzene ring
1685.79	1669.8	-C=O stretching of carbonyl group
1434.00	1490.9	-CH2 stretching
1201.65	1263.6	-C-S stretching of esters
1099.43	1088.4	-N-H stretching of secondary amino group
1026.13	1013.8	-C-O stretching of carbonyl group
754.17	752.9	-OH bending of SO_3H

The spectrum of clove in Figure 2 shows a characteristic broad absorption band at 3276.3 cm^{-1}, a weak peak was observed at 2922.2 cm^{-1} and a very small peak at 1684.8 cm^{-1} while the weak peak at 1319.5 cm^{-1}. The spectrum of ginger alone as displayed in Figure 3 shows different absorption bands ranging from the characteristic broad peak at 3265.1 cm^{-1}, a medium weak peak at 2929.7 cm^{-1}, a small weak peak at 1561.8 cm^{-1} another medium absorption peak at 1148.0 cm^{-1} and a sharp peak at 995.2 cm^{-1}. Figure 4 showing the spectrum of turmeric alone displays a broad band at 3257.7 cm-1, small peaks at 2922.2 cm^{-1} and 1595.3 cm^{-1} and a medium peak at 1342.0 cm^{-1}. Another very small peak was observed at 1077.2 cm-1 in addition to another medium peak at 998.9 cm^{-1}.

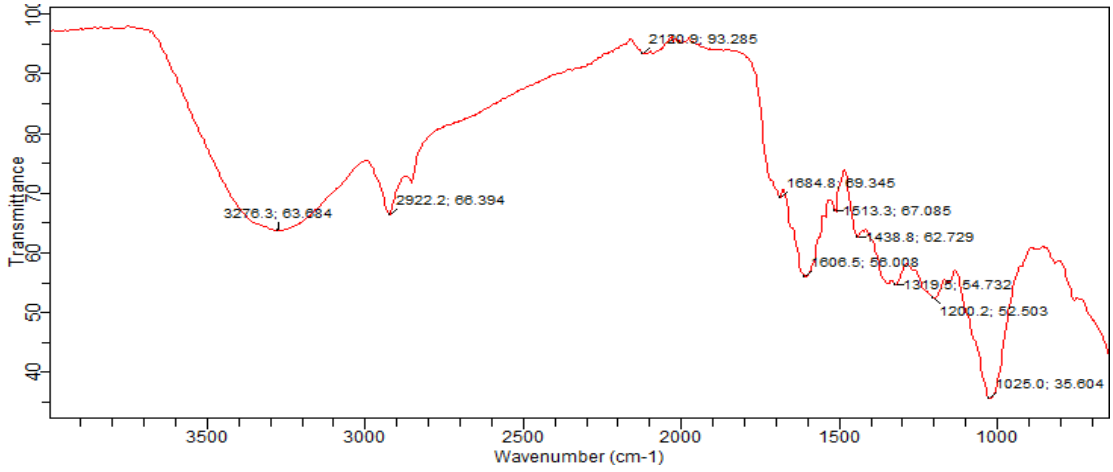


Figure 2. FTIR spectrum of clove alone.

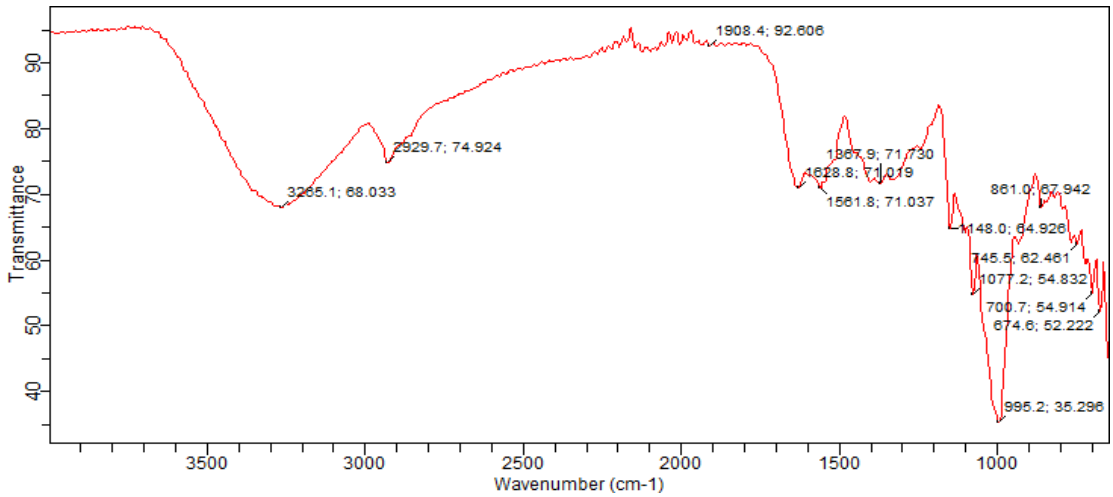


Figure 3. FTIR spectrum of ginger alone.

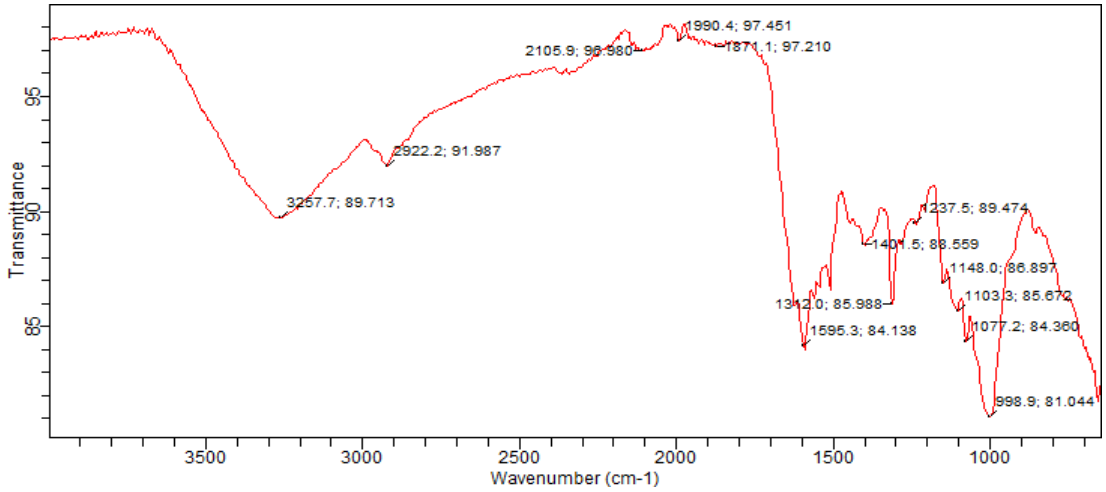


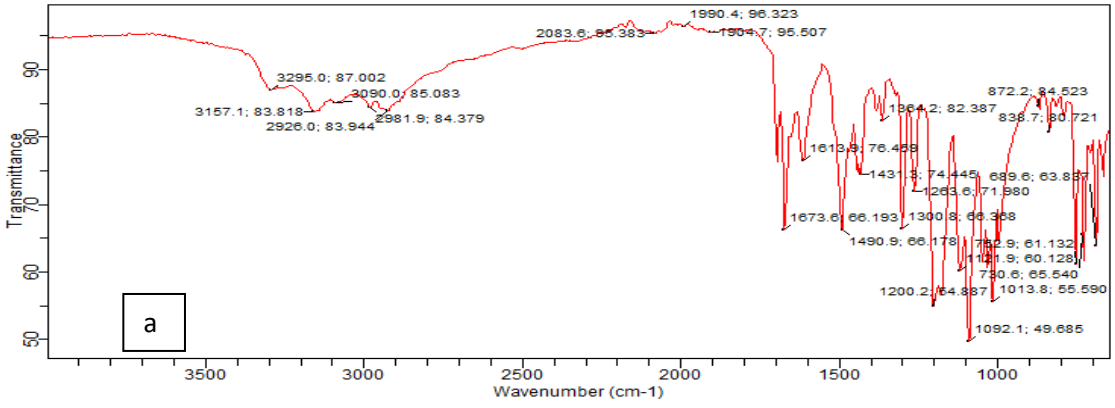
Figure 4. FTIR spectrum of turmeric alone.

The spectra of 50:50 combination of amlodipine with clove, ginger and turmeric are displayed below as Figures 5a, 5b and 5c respectively. It shows characteristic groups of amlodipine and these are confirmed in Table 2 which reveals the positions of the wavenumbers of some of the observed functional groups.

Table 2. Overview of characteristic FTIR peaks of amlodipine and its position in combination with clove, ginger and turmeric

Observed peaks of amlodipine	Observed peaks of AC	Observed peaks of AG	Observed peaks of AT	Functional groups corresponding to peaks
3295.0	3295.0	3287.5	3291.2	-N-H stretching of primary amino group
3153.3	3157.1	3145.3	3157.1	-OH stretching of SO_3H
2981.9	2981.9	2981.9	2981.9	-C-H stretching of benzene ring
1669.8	1673.6	1673.6	1673.6	-C=O stretching of carbonyl group
1490.9	1490.9	1490.9	1490.9	-CH2 stretching
1263.6	1263.6	1263.6	1263.6	-C-S stretching of SO_3H
1088.4	1092.1	1092.1	1092.1	-N-H stretching of secondary amino group
1013.8	1013.8	1013.8	1013.8	-C-O stretching of carbonyl group
752.9	752.9	752.9	752.9	-OH bending of SO_3H

AC = 50:50 combination of amlodipine and clove; AG = 50:50 combination of amlodipine and ginger; AT = 50:50 combination of amlodipine and turmeric.



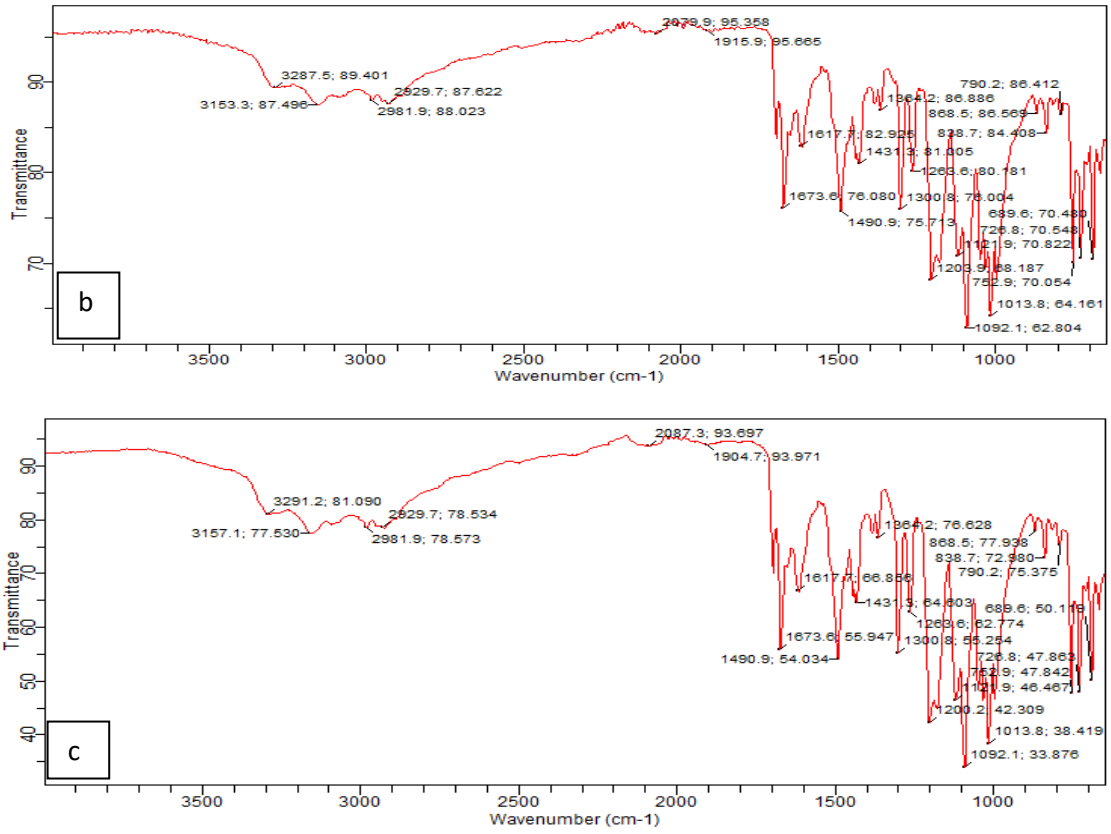


Figure 5. FTIR spectrum of combination of amlodipine and clove (a), spectrum of combination of amlodipine and ginger (b), spectrum of combination of amlodipine and turmeric (c).

2.2. Differential Scanning Calorimetry (DSC) analysis

Figure 6 shows the thermogram amlodipine alone has a sharp endothermic peak. The integrated DSC parameters of pure amlodipine, clove alone, ginger alone and turmeric alone presented in Table 3 shows the onset and endset melting point od amlodipine to be between 131.28 °C and 138.97 °C respectively. Its peak melting temperature was at 135.97 °C, the enthalpy of fusion (ΔH) was 487.62 J/g and the temperature range (ΔT) was 7.69 °C.

Table 3. DSC Parameter of Amlodipine, Clove, Ginger and Turmeric

Parameter	A	C	G	T
Onset temperature (°C)	131.28	81.60	38.31	59.29
Peak temperature (°C)	135.97	142.61	81.06	63.73
Endset temperature (°C)	138.97	156.96	249.59	68.41
Enthalpy of gelatinization (J/g)	487.62	330.78	387.53	835.29
ΔT (°C)	7.69	75.36	211.28	9.12

A = data for pure amlodipine; C = data for clove alone; G = data for ginger alone; T = data for turmeric alone

The thermogram of clove as displayed in Figure 7 shows a first broad endothermic peak around 142.61 °C and a second smaller endothermic peak around 210 °C. In addition, two exothermic peaks were observed; the first exothermic peak was mild but wide at 330 °C while the other strong and sharp exothermic peak was observed at 475 °C. The energy of fusion as displayed in Table 3 associated with changes in the inter and intramolecular bonds within the clove moiety was 330.78 J/g while the temperature range; ΔT was 75.36 °C.

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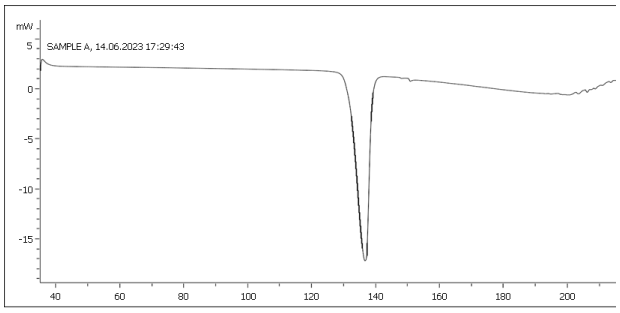

Figure 6. DSC thermogram of pure amlodipine.

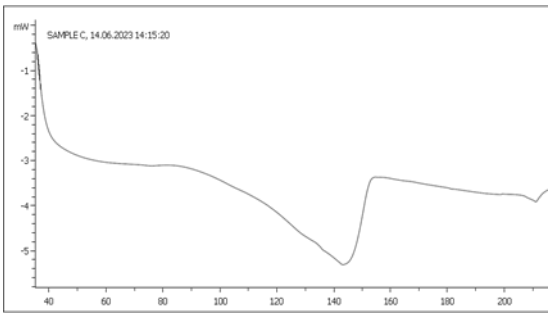

Figure 7. DSC thermogram of clove alone.

Figure 8 shows the thermogram of ginger with a very broad thermogram and no visible peak. However, from the integrated data (Table 3), the peak was observed to be 81.06 °C with the onset of melting occurring at 38.31 °C and the endset melting occurring at 249.59 °C. The enthalpy of fusion (387.53 J/g) was similar to that observed in clove and the temperature range was 211.28 °C. The thermogram of turmeric displayed in Figure 9 on the other hand shows a sharp peak at 63.73 °C, Table 3 shows the onset temperature of melting at 59.29 °C and a endset melting temperature of 68.41 oC. The enthalpy of fusion was very high (835.29 J/g) while the temperature range (9.12 °C) was observed to be very narrow.

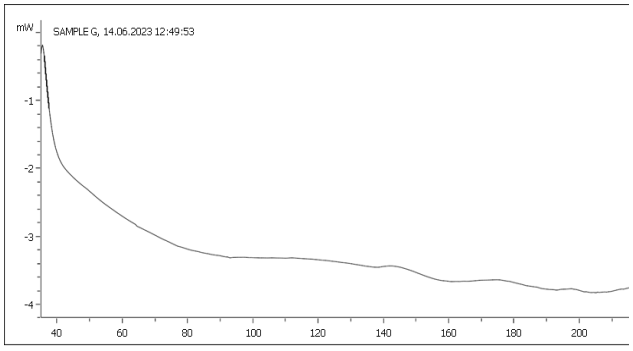

Figure 8. DSC thermogram of ginger alone.

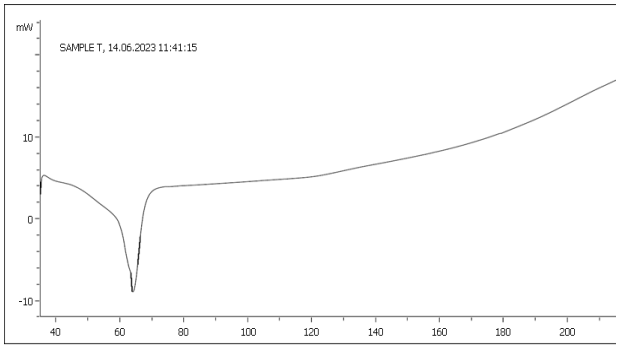

Figure 9. DSC thermogram of turmeric alone.

The thermogram of 50:50 combination of amlodipine with clove, ginger and turmeric are displayed as Figures 10a, b and c respectively. The integrated data of the DSC parameters for the drug-spice combination is also presented in Table 4. An early onset of melting was observed at 35.34 °C which is lower than that of pure amlodipine or clove and an endset melting temperature of 227.42 °C which is higher than that observed with pure amlodipine or clove alone. The enthalpy of fusion 231.61 J/g while the temperature range (192.08 °C) was wider than that of amlodipine or clove alone.

The thermogram of the combination of amlodipine and ginger as displayed in Figure 10b shows broadening and shifting of a melting peak between 135.97 °C to 182.20 °C. Several other smaller and broad peaks were also observed in this thermogram. Table 4 shows the onset of melting to be 162.23 °C, the endset temperature was 201.98 °C. The enthalpy of fusion was 447.05 J/g while ΔT was 39.75 °C.

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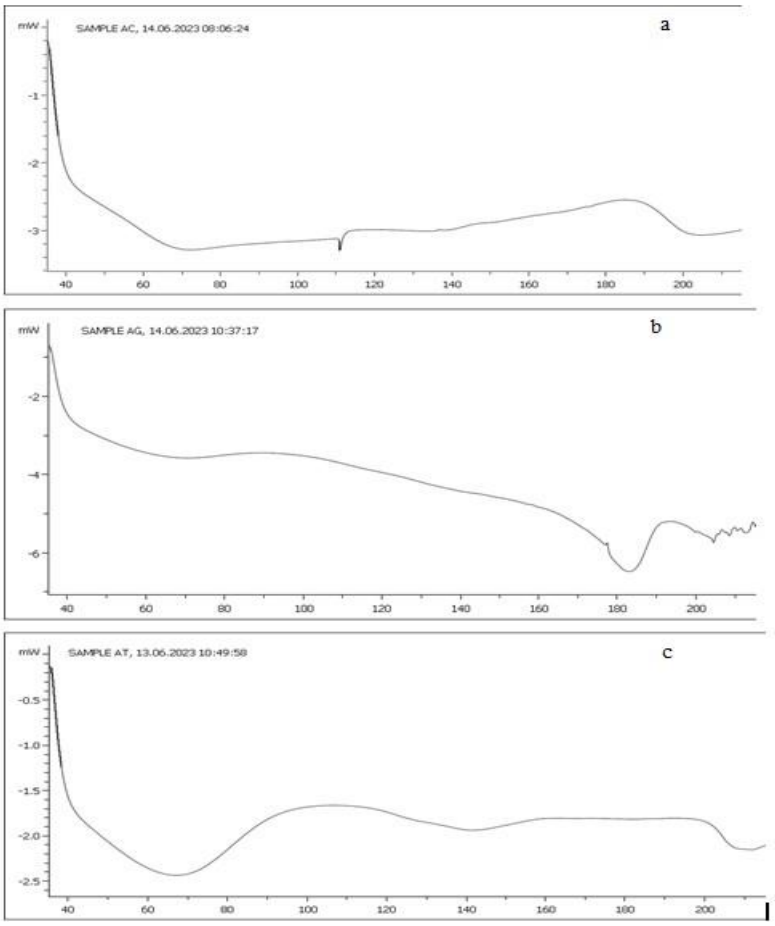

Figure 10. DSC thermogram of 50:50 combination of amlodipine and clove (a), thermogram of 50:50 combination of amlodipine and ginger (b), thermogram of 50:50 combination of amlodipine and turmeric (c).

The combination of amlodipine and turmeric shows lower onset melting temperature (35.57 °C) than those of amlodipine alone or turmeric alone. The endset temperature was also reduced (111.80 °C) compared to amlodipine alone but higher than that of turmeric alone. The melting peak due to amlodipine was not observed in this combination. The enthalpy of fusion for the combination of amlodipine and turmeric was observed to be drastically lower (182.94 J/g) than that of amlodipine alone (487.62 J/g) and significantly lower than that of turmeric alone (835.29 J/g). The temperature difference between the onset and the endset/conclusion of melting here was observed to be higher (9.12 °C) but somewhat similar to that of pure amlodipine (7.69 °C). The temperature difference between the onset and the conclusion of melting here was observed to be higher (9.12 °C) but somewhat similar to that of pure amlodipine (7.69 °C).

Table 4. DSC parameter of amlodipine alone and amlodipine combined with clove, ginger or turmeric

Parameter	A	AC (50:50)	**C**	AG (50:50)	G	**AT (50:50)**	**T**
Onset temperature (°C)	131.28	35.34	81.60	162.23	38.31	35.57	59.29
Peak temperature (°C)	135.97	69.23	142.61	182.20	81.06	63.76	63.73
Endset temperature (°C)	138.97	227.42	156.96	201.98	249.59	111.80	68.41
Enthalpy of gelatinization (J/g)	487.62	231.61	330.78	447.05	387.53	182.94	835.29
ΔT (°C)	7.69	192.08	75.36	39.75	211.28	76.23	9.12

AC (50:50) = combination of amlodipine and clove in the ratio 50:50; AG (50:50) = combination of combination of amlodipine and ginger in the ratio 50:50; AT (50:50) = combination of amlodipine and turmeric in the ratio 50:50.

3. DISCUSSION

Fourier Transform Infrared (FT-IR) spectrophotometer is an effective analytical technique that is used to assess compatibility between materials. They make use of the different functional groups in the

compounds which absorb at different bands or wavelengths. Any significant change or disappearance in location or structure of the absorption band indicate potential interactions or incompatibility [12].

The spectrum of amlodipine alone displayed in Figure 1 showed the presence of ≡C-H stretch of primary amines and OH stretching of SO_3H. The characteristic C-H stretching of the benzene ring of amlodipine, C=O stretch of amide group and vibrations of esters bonds were also noted. These characteristic absorption bands are linked to the presence of alkynes, alkenes, sulfonic acid and esters which are characteristic of amlodipine as shown in Table 1 [13- 15].

The spectrum of clove alone revealed bands that suggest the presence of -OH group of phenols and alcohols, -CH_2 and -CH_3 of alcoholic compounds, -C=O stretch of ketone groups and vibrations of aromatic esters. These bands observed in Figure 2 are consistent with those reported by some other authors [16, 17].

The FTIR spectrum of ginger alone as displayed in Figure 3 reveals vibration of -OH groups, the presence of saturated hydrocarbons alkanes and carbonyl groups (-C=O). These absorption bands are linked to the presence of compounds that are characteristic of ginger [18, 19].

Figure 4 showing the spectrum of turmeric alone reveals the presence of -OH group of phenol and absorption bands corresponding to aromatic skeletal stretching vibration. These characteristic groups/compounds are consistent with those reported by other researchers for turmeric [20, 21].

The 50:50 combination of amlodipine with each of the spices; clove, ginger and turmeric returned the spectra displayed in Figures 5a, b and c respectively. The figure shows all the characteristic peaks of amlodipine earlier outlined are present in the spectra of amlodipine-spice combination with no significant changes or losses in these characteristic groups.

However, the combination with turmeric showed lower peak intensities than the combination with the other two spices (clove and ginger) especially at the fingerprint region but shifts in wavenumbers, reduction in intensity, broadening have been linked to effects of mixing or dilution and not necessarily a result of incompatibility or interaction [22]. Only slight shifts in wavenumbers of characteristic functional groups of the spices were observed from the spectra. Overall, there are no observed significant changes in the absorption bands, no overlap of absorption peaks, no appearance of new peaks, no disappearance of peaks in the spectra. Therefore, it can be deduced that no chemical incompatibilities nor interaction occurred in the combinations of amlodipine and clove, ginger or turmeric.

DSC is a thermal analysis technique in which the heat flow into or out of a sample is measured as a function of temperature or time while the sample is exposed to a controlled temperature program. In other words, DSC provides direct assessment of the heat energy uptake, which occurs in a sample within a regulated increase or decrease in temperature. It is a very powerful technique for the identification of various physical properties and thermal transitions of materials. With the DSC, it is possible to observe fusion and crystallization events, glass transition temperature, melting, crystallization, specific heat capacity, cure process, oxidation behaviour, determine purity and thermal stability of materials [23, 24].

The principle governing this technique is based on the fact that, when the sample undergoes physical transformation such as phase transitions, these transitions involve energy changes or heat capacity changes that can be detected by DSC with great sensitivity. DSC gives an insight into speedy selection of potential inclusion materials during formulation development [25].

The DSC thermogram displayed as in Figure 6 shows the sharp endothermic peak of amlodipine which signifies the amount of heat absorbed by the drug molecule. The sharp endothermic peak of amlodipine observed in Figure 6 signifies the amount of heat absorbed by the drug molecule. The melting and decomposition of the drug molecule is deduced from the parameters presented in Table 3. In this study, the peak melting temperature of amlodipine (135.97 ^oC) was observed to be different from some other studies which reported the melting peak of amlodipine to be between 202 ^oC and 206 ^oC [26, 27]. However, one other study reported similar melting peak of amlodipine (142.32 ^oC) Jiang [28]. These differences may be due to differences in the sourced materials (different manufacturers) and probably the presence of impurities.

Two broad endothermic peaks were observed in the thermogram of clove alone (Figure 7), the second smaller endothermic peak is attributed to baseline shifts may be related to changes in the sample weight due to decomposition or specific heat of the sample due to melting [29]. A similar report showing two exothermic peaks of clove has also been reported [30]. The peak melting temperature of clove as displayed in Table 3 was somewhat similar to earlier reports [31, 32]. The energy of fusion associated with changes in the inter and intramolecular bonds within the clove moiety was observed to be minimal compared to the other spices. The temperature range between the onset and end of melting was wide indicating that there is a wide

temperature difference between the beginning of melting and the conclusion of melting of the drug molecule. This suggests that very high temperature is required to decompose the clove moiety.

The integrated data of ginger (Table 3) was observed to be different from an earlier report [30] where they described a mild exothermic peak of ginger at 290 °C and a stronger peak at 460 °C. In this study, a very broad endothermic peak was observed which correlates to transition from glass to rubbery state. The enthalpy of fusion of ginger was similar to that of the clove moiety, but the temperature range between the onset and endset of melting was about three times higher than that of clove. This indicates that a wide temperature range is required to bring about decomposition of ginger suggesting that ginger is more stable than the other spices.

The onset temperature of melting of turmeric was lower than that of clove but higher than that of ginger but the endset melting temperature was lower than both clove and turmeric. Very high transition temperature was observed to break the bonds in turmeric compared to the other spices. However, minimal temperature would be required to bring about decomposition of turmeric with very high extent of decomposition suggesting that turmeric is not thermally stable. According to Table 3, turmeric is less stable than clove or ginger.

The combination of amlodipine with clove shows lower peak melting temperature than that observed for the pure drug alone or for clove alone (Table 4). This shift and change in melting temperature peaks may be an indication of some form of interaction as a result of combination of amlodipine with clove. The enthalpy of fusion was found to be reduced drastically from that observed for the pure drug which indicates weak bond order in the combination of amlodipine and clove. This suggests that lower temperature is required to cause decomposition in this combination.

The thermogram for the combination of amlodipine and ginger shows the presence of amlodipine melting peak. The onset event of melting and the endset temperature were higher than those of amlodipine or ginger alone. These major changes in the temperature of the different events may be indicative of some form of interaction due to combination of the drug and ginger. Interestingly, the enthalpy of fusion was similar to that of pure amlodipine suggesting that decomposition occurred at about the same temperature in both scenarios. The temperature difference between the onset and endset of melting of this recipe was significantly higher than that of pure amlodipine.

The characteristic peak of amlodipine was observed to have disappeared in the thermogram of the combination of amlodipine and turmeric which suggests indication of interaction between the drug and the spice. The enthalpy of fusion for the combination of amlodipine and turmeric was observed to be drastically lower than that of amlodipine alone and significantly lower than that of turmeric alone. This suggests high amount of heat is required to bring about the decomposition of this drug-spice combination.

From the results, it can be observed that all the spices impact on the thermal stability of amlodipine to varying degrees but the combination containing clove and turmeric appeared to present the most impact in relation to the stability of amlodipine.

4. CONCLUSION

Compatibility studies of two or more drugs or the study of drugs and excipients are essential for prediction of drug stability. In this study, the compatibility of amlodipine with clove, ginger and turmeric was assessed by a non-thermal technique: Fourier Transform Infrared (FT-IR) and a thermal technique: Differential Scanning calorimetry (DSC). No tangible evidence of interaction was observed from the FTIR studies however, DSC showed that clove, ginger and turmeric in combination with amlodipine affects the stability of amlodipine. The indications of incompatibility were more pronounced in the amlodipine-clove and amlodipine-turmeric combinations. The data provided in this study are important as an advisory showing the possible adverse effect on the thermal stability of amlodipine in the presence of clove, ginger or turmeric.

5. MATERIALS AND METHODS

5.1. Materials

Dried clove buds, dried ginger roots and dried turmeric roots were purchased from Orange market in Mararaba, Nasarawa State, Nigeria, Amlodipine besylate was donated by a pharmaceutical company in Nigeria, Distilled water was prepared in the Department of Pharmaceutics and Pharmaceutical Technology, Bingham University, Karu, Nasarawa State, Nigeria.

5.2. Methods

5.2.1. Preparation of the Selected Spices

The purchased spices (clove, ginger, turmeric) were cleaned and pulverized using a ball mill. Aqueous extracts of these spices were prepared by macerating the dried materials in distilled water at room temperature at ratio of 1:10. The macerate was filtered using a muslin cloth, the filtrate was concentrated over a water bath (DFS KW- 1000DC HH4 PEC Medical USA) and thereafter dried in the hot-air oven between 40 – 50 ^{o}C. The resulting dried powder was blended in an electric blender (Sarah Tech Model RL-1301 BMS) to reduce the particle size and then stored in a desiccator for subsequent use in the study.

5.2.2. Fourier Transform InfraRed (FT-IR) Studies

The powdered spices and amlodipine at a ratio of (50:50) were individually triturated with potassium bromide and compressed into pellets (1 ton/cm^2). InfraRed spectra were obtained between 4000 – 400 cm^{-1} from the Cary 630 Fourier transform infrared (FT-IR) Spectrometer, (Agilent Technologies, USA). All spectra were collected with a resolution of 8 cm^{-1} and background registration of 16 scans were added and averaged to improve the noise to signal ratio.The different spectra were compared for possible interaction or reactions.

5.2.3. Differential Scanning Calorimetry (DSC) Analysis

Samples of amlodipine alone, each of the spices alone (clove, ginger, turmeric), and the combination of amlodipine and spices were placed in the aluminum pans of the differential scanning calorimetry (Model DSC 204 F1Netzsch, Germany). The pans were crimped and heated between 60 and 300 ^{o}C at a scanning rate of 10 ^{o}C/min under constant nitrogen flow of 20 mL/min.

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