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Comparison of Solid-state and Solution-based Synthetic Reactions of Copper Complexes of two Anti-inflammatory Drugs with their Antibacterial Activity Studies

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Abstract

Comparative study of the synthesis of copper complexes $[Cu(IBU)_2(H_2O)_2]Cl_2$ **(1),** and $[Cu(ASP)_2(CH_3COO)_2]$ **(2)** using solvent-free and solvent-based techniques was carried out. Complexes **1** and **2** obtained were characterized using Fourier Transform –Infrared, Ultraviolet-Visible spectroscopies and powder X-ray Diffractometry analyses. Analysis of spectral data revealed that Ibuprofen and Aspirin coordinated with copper ion through both oxygen atoms of the hydroxyl and carbonyl groups, with both ligands acting as bidentate. Two molecules of water coordinated with the copper ion forming an octahedral geometry in **1**, with a chloride ion outside the coordination sphere. Two acetate molecules coordinated with copper ion forming an octahedral geometry in **2**. *In-vitro* antibacterial activity of the complexes was found to be higher than those of the starting materials. Comparative study of the two methods used to synthesize these complexes showed that the solvent free-synthetic technique presented higher efficiency in terms of energy and time than the conventional solvent-based, as there was no need for the application of heat and also the reaction was completed within a short time. Thus, the solvent-free technique appears to be more effective for the synthesis of the Cu (II) complexes of Ibuprofen and Aspirin.

Keywords: Solvent-free, Solvent-based, Ibuprofen, Aspirin, Antibacterial activity.

1. Introduction

Ibuprofen and Aspirin constitute an important group of heterocyclic compounds, having valuable biological activity in the area of medicine (Koskimaki *et al.*, 2006). They have found their uses as anti-inflammatory agents. They provide a binding mode similar to that of non-

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nucleoside reverse transcriptase inhibitors (NNRTIs) (Chen *et al.,* 1991). Chemically, Ibuprofen is a 2-arylpropionate derivative, and is characterized by stereocenter in the α-position of the propionate moiety. It is useful in medical practice for the relief of symptoms of arthritis, dysmenorrheal, and antiplatelet effect in the blood. It inhibits the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H_2 (PGH_2) (Rao *et al.,* 2008).

Aspirin, on the other hand, is a derivative of salicyclic acid. It is useful in the area of medicine for the treatment of fever, inflammation, swelling, for the relief of headache and minor ailments (Sneader, 2000). It has been reported that copper compounds present interesting antimicrobial properties, and they have been extensively studied in recent years (Abass *et al.,* 2018; Katugampala *et al.,* 2018). This, coupled with the non-toxic nature of copper, informed the choice of the development of copper complexes for this present study. The synthesis of copper (II) aspirinate, $[Cu_2(ASP)_4]$ from Cu(II) and Aspirin was reported by Fujimori *et al*. (2005). The *in-vitro* inhibitory activity study showed that the $[Cu_2(ASP)_4]$ complex exhibits significant antipyretic activity (Fujimori *et al.,* 2005). $[Cu_2(ASP)_4]$ complex was also synthesized by conventional method and its effects on rat Thrombosis and Neutrophils were investigated. The in-vitro inhibitory activity study on rat thrombosis showed that the aspirin-copper complex exhibits significant antithrombotic and neutrophilic activities on the organs and cells of the rat (Zhi-qiang *et al.,* 2004).

Moreover, various reports on the conventional method of synthesizing heterocyclic compounds (such as Ibuprofen and aspirin) have shown that the method usually leads to the coexistence of the starting materials in solution or volatile organic solvents (VOCs) and consequently, this method could lead to an acute problem of chemical waste and low yield of the product (Abuhijleh, 1997; Domiza *et al.,* 2001; Zhi-qiang *et al.,* 2004; Fujimori *et al.,* 2005; Bojidarka, 2007; Kafarska *et al.,* 2009; Shaker *et al.,* 2009).

Much attention has been paid to the development of new methods for synthesizing heterocyclic compounds, due to their potential importance in the pharmaceutical fields and inorganic coordination chemistry (Poliakoff and Licence, 2007). Non-conventional method of synthesis (solvent-free synthesis) now serves as a new method for synthesizing heterocyclic compounds, because it leads to environmentally benign procedures that minimize waste productions, considerably improve the yield of product, save energy and time, and are of high interest from both economical and synthetic points of view (Reed and Hutchison, 2000; Balema *et al.,*

2002; Ren *et al.*, 2003; Kaupp, 2006; Sheldon and Arends, 2006; Braga *et al.*, 2008; Swinburne and Steed, 2009; Tella *et al.*, 2010b).

Previously, our group communicated a preliminary report on the solvent-free synthesis of Ni (II) and Co (II) complexes of cimetidine (Tella *et al.*, 2011), Cu(II) complexes of non-steroidal anti-inflammatory drugs, caffeine and codeine (Tella *et al.*, 2014a), Cu(II) and Zn(II) complexes of anthranilic acid (Tella *et al.*, 2014b) and Cu(II) complexes of 3,4,5-trihydroxybenzoic acid (Adimula *et al.*, 2017). We demonstrated that the solvent-free reactions by grinding the stating materials in a mortar with pestle rapidly led to complete reactions in several minutes at ambient temperature, and the product yields were quantitatively high.

In continuation of our research, we hereby report the solid-state synthesis of copper(II) complexes of Ibuprofen and Aspirin using an agate mortar with pestle and by ball-milling for several minutes at ambient temperature. Solvent-based technique was also used for the synthesis of the same complexes, for comparison with the solid-state products. The products were characterised; the analytical and spectral data of the products obtained from the solvent-free methods were compared with those of the free ligands and the solution-based products.

2. Materials and Methods

2.1. Materials and Instrumentation

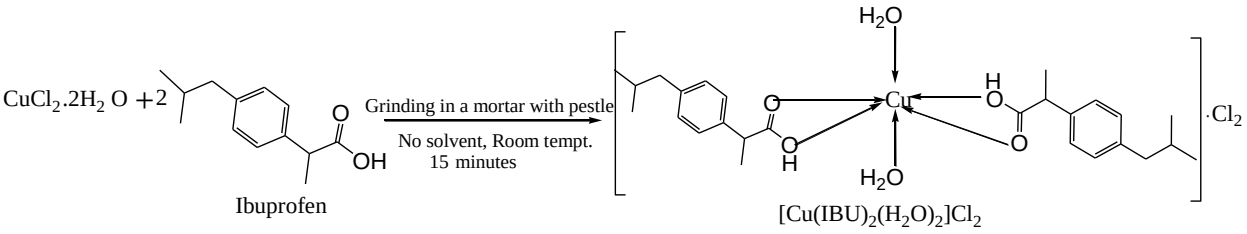
All reagents and chemicals were of analytical grade and used as obtained from SigmaAldrich (Germany). The ligands (Ibuprofen and Aspirin) were obtained as a gift from Tuyil Pharmaceutical Company, Ilorin. FT-IR spectra of the ligands and the complexes were recorded in the form of KBr pellets in the range of 4000–400 cm^{-1} using a Perkin Elmer FTIR spectrometer. Electronic spectra were done on an Aquamate Spectrophotometer, Model V4.60. Conductivity measurements were carried out using a WTW Conductimeter Bridge. Thin-layer chromatography was carried out using TLC plates coated with silica gel. AAS analysis was carried out on Atomic Absorption Spectrophotometer Model Jenway 6503. X-ray diffraction analysis was carried out on a Bruker AVS D8 graphite diffractometer. Elemental analysis was performed on a Perkin-Elmer CHN Analyzer 2400 Series II. *Escherichia coli, Staphylococcus aureus,* and *Klebsella pneumonia* were obtained as fresh isolate from the University of Ilorin Teaching Hospital, Ilorin.

2.2 Experimental Procedure

The methods described by Stuart *et al.* (2006) and Braga *et al.* (2008) were modified and adapted for the mechanochemical (solvent-free) synthesis, and the method described by Tella and Obaleye (2009, 2010a) was modified and adapted for solution-based synthesis. The stoichiometry of reactants used was in the ratio of 1:2 metal to ligand (Tella and Obaleye, 2009).

2.2.1. Solid-state synthesis of $[Cu(IBU)_2(H_2O)_2]Cl_2$ (1a):

Ibuprofen (2 mmol, 0.413 g) and copper chloride ($CuCl_2.2H_2O$) (1 mmol, 0.170 g) were weighed into a mortar that has been previously washed and dried. The reactant mixture was then ground continuously with pestle for 15 minutes to fine powder at room temperature. The progress of the reaction was monitored by Thin-Layer Chromatography (TLC) until no traces of reactants were found. Sky-blue powder obtained was washed with methanol to remove unreacted starting materials and dried at ambient temperature. The equation of reaction is shown in Scheme 1 below:



Scheme 1: Equation of reaction for mechanochemical synthesis of $[Cu(IBU)_2(H_2O)_2]Cl_2$

Yield: 96.2%, Anal. cald M.wt. = 615 g/mol, M.pt = 122 ^oC. Anal.calcd (Found) % for ($C_{26}H_{36}Cl_2O_8Cu$); C, 50.81 (50.70); H, 5.86 (5.67); Cu, 10.26 (10.21); IR (KBr, cm^{-1}): 3446, 3336, 3022, 2972, 1787, 1575, 1419, 599; UV-Vis (DMSO) λ_{max}DMSO,nm: 547.

2.2.2 Solvent-based synthesis of $[Cu(IBU)_2(H_2O)_2]Cl_2$ (1b):

A solution of ibuprofen (2 mmol, 0.413 g) in methanol (10 ml) was added to a solution of copper chloride ($CuCl_2.2H_2O$) (1 mmol, 0.170 g) in methanol (10 ml). The resulting solution was refluxed for 1 hour at 70 ^oC, filtered, and allowed to evaporate for 2 days at ambient temperature. Crystalline pale blue solid was obtained, washed with methanol and dried at ambient temperature. The equation of reaction is shown in Scheme 2 below:

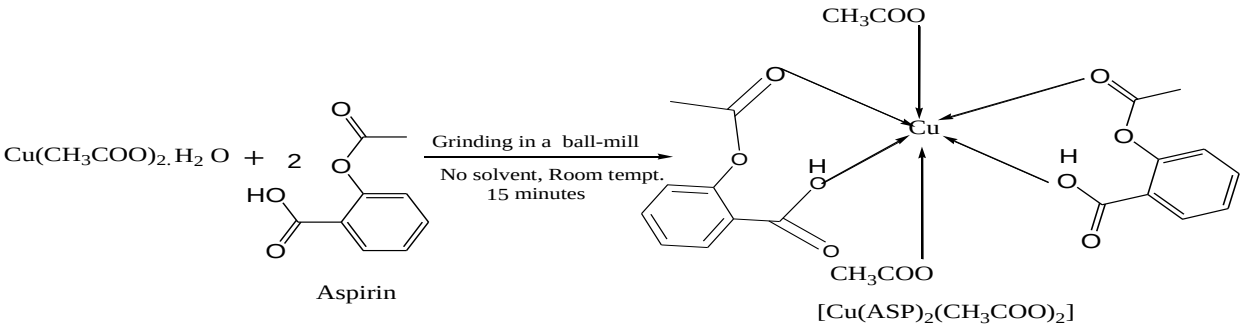
$$CuCl_2.2H_2O + \text{Ibuprofen} \xrightarrow[\text{Methanol, 1 hr}]{\text{Reflux}} [Cu(IBU)_2(H_2O)_2]Cl_2$$
$$70\,^{\circ}C$$

Scheme 2: Equation of reaction for solvent-based synthesis of $[Cu(IBU)_2(H_2O)_2]Cl_2$

Yield: 68.9%, Anal. calcd M.wt. = 615 g/mol, M.pt = 125 ^{o}C. Anal.calcd (Found) % for ($C_{26}H_{36}Cl_2O_8Cu$); C, 50.81 (50.60); H, 5.86 (5.67); Cu, 10.25 (10.21); IR (KBr,cm^{-1}): 3448, 3338, 3022, 2995, 1785, 1579, 1419, 704; UV-Vis(DMSO) λ_{max}DMSO,nm : 538.

2.2.3. Solid-state Synthesis of $[Cu(ASP)_2(CH_3COO)_2]$ (2a):

Aspirin (2 mmol, 0.360 g) and copper acetate ($Cu(CH_3COO)_2.H_2O$) (1 mmol, 0.199 g) were weighed into a locally made ball-mill equipped with each of four grinding steel balls (10 g). The planetary ball-mill was washed and dried before use. The reactant mixture was then mixed in the planetary ball-mill continuously for 15 minutes to a fine powder at ambient temperature. The progress of the reaction was monitored by Thin-Layer Chromatography (TLC) until no traces of reactants were found. Blue powder obtained was washed with methanol to remove unreacted starting material and dried at room temperature. The equation of reaction is shown in Scheme 3 below:



Scheme 3: Equation of reaction for mechanochemical synthesis of $[Cu(ASP)_2(CH_3COO)_2]$

Yield: 93.1%, Anal. cald M.wt. = 605 g/mol, M.pt = 180 ^{o}C. Anal.calcd (Found) % for ($C_{20}H_{22}O_{16}Cu$); C, 43.63 (43.58); H, 3.63 (3.53); Cu, 10.41 (10.40); IR (KBr,cm^{-1}): 3489, 2999, 2970, 1753, 1575, 1419, 1039, 667, 646, 543. UV-Vis, λ_{max} DMSO,nm: 667.

2.2.4. Solvent-based Synthesis of $[Cu(ASP)_2(CH_3COO)_2]$ (2b):

A solution of aspirin (2 mmol, 0.360 g) in methanol (10 ml) was added to a solution of copper acetate ($Cu(CH_3COO)_2.H_2O$) (1mmol, 0.199 g) in methanol (10 ml). The resulting solution was refluxed for 1 hour at 70 ^{0}C, filtered, and allowed to evaporate slowly for 2 days at

ambient temperature. Crystalline bluish green solid was obtained, washed with methanol and dried at ambient temperature. The equation of reaction is shown in Scheme 4 below:

$$Cu(CH_3COO)_2 \quad + \quad \text{Aspirin} \xrightarrow[\text{Methanol, 1 hr}]{\text{Reflux}} [Cu(ASP)_2(CH_3COO)_2]$$
$$70^0C$$

Scheme 4: Equation of reaction for Solvent-based synthesis of $[Cu\ (ASP)_2(CH_3COO)_2]$

Yield: 62.7%, Anal. cald M.wt. = 604.6 g/mol, M.pt = 182 ^{0}C. Anal.calcd % for ($C_{20}H_{22}O_{16}Cu$); C, 43.63(44.03); H, 3.63(3.54); Cu, 10.41(10.43); IR (KBr, cm^{-1}): 3489, 2993, 2964, 1755, 1575, 1419, 1039, 667, 646. UV-Vis, λ_{max} DMSO, nm: 667.

2.3 Antibacterial Activity Studies

Antibacterial activity studies of Ibuprofen and Aspirin with their complexes were determined using agar well diffusion method described by Wasi and Sigh (1987) and Johansson *et al.* (2007). Solutions of two different concentrations (50 µg/ml, and 25 µg/ml) consisting of ibuprofen, aspirin and the two complexes were prepared in methanol and ethanol. 10 g of Muller–Hinton agar was dissolved in 250 ml distilled water and autoclaved at 70 ^{o}C for 15 minutes. 20 ml of the media was transferred into previously sterilized petri-dish and allowed to solidify at ambient temperature. Bacterial inocula incubated for 24 hours and autoclaved at 70 ^{o}C for 15 minutes were spread on the surface of Muller-Hinton agar media with the help of a sterile cotton swab. Four wells were dug in the media with the help of a sterile cork borer (5 mm of internal diameter) with centers at least 24 mm apart and each well in each plate was then filled with 100 µl of test solutions. The plates were left undisturbed on the bench for 2 hours at ambient temperature. The plates were subsequently incubated at 35 ^{o}C temperature for 24 hours. The antibacterial activity was determined by measuring the zones of complete inhibition diameter in millimeters (mm) using a ruler and a 5 mm diameter paper discs. Triplicate measurements were performed.

3. Results and Discussion

Analysis of the UV-Visible and FT-IR spectra clearly showed the formation of $[Cu(IBU)_2(H_2O)_2]Cl_2$ (**1a and 1b)** in ratio 1:2 (metal: ligand). It also appears from the results that the solvent-free method of synthesis gave similar spectral data in comparison with the solution-based method. The elemental analysis for C, H, N was also found to be consistent with the formular units of the products (**Table 1**).

Also, both complexes, $[Cu(ASP)_2(CH_3COO)_2]$ (**2a and 2b)** show interesting properties that have been correlated with those in the literature (Mariam *et al.*, 2010; Sokolik *et al.*, 2006).
The analytical data of complexes **1** and **2** obtained via the two different methods are shown in Table 1 below.

The parent ligands, ibuprofen and aspirin, are white whereas the complexes **1** and **2** are coloured, ranging from sky blue, pale blue, blue and bluish green. All the products are stable, non-hygroscopic, soluble in methanol, ethanol and DMSO. The molar conductivity values of 10^{-3} M solution of DMSO of the complexes at 25 ^oC are 102 and 105 Ω^{-1} mol^{-1} cm^2 for **1a** and **1b** respectively; and 50.3 and 52.6 Ω^{-1} mol^{-1} cm^2 for **2a and 2b** respectively. These data showed that complexes **1a** and **1b** are electrolytes and **2a** and **2b** are non-electrolytes. The test for chloride was carried out by the addition of 1ml of $AgNO_3$ to 1mg of **1a** and **1b** (Abuhijleh, 2007). The test was positive with the formation of white precipitate indicating the chloride is outside the coordination sphere. In an attempt to test for the presence of coordinated water, both complexes **1** and **2** were activated at 110 ^oC for 15 minutes and the reaction progress was monitored by using FT-IR spectroscopy (Mariam *et al.*, 2010). From the study, there was no change in the composition and vibration frequency of **1a** and **1b**. This indicated that H_2O is coordinated with the metal ion inside the coordination sphere, and is not present as lattice water. The test for acetate was also carried out by the addition of 1ml of 2.0M H_2SO_4/H_2O ($1:1^v/_v$) to 1 mg of **2a** and **2b** (Angiolini *et al.*, 2009). There was no formation of any precipitate and there was no observation of vinegar odour. This indicated that the acetate is inside the coordination sphere. The R_f values for complexes **1** and **2** obtained via both methods showed single spot indicating the purity of the mechanochemically synthesized complex. Also, the percentage yields of the mechanochemical products of **1** and **2** are higher than the solvent-based products, melting points of the complexes are also higher than those of the parent ligand. All these results indicate successful synthesis using the solvent-free and solvent-based methods and that the complexes obtained from both methods are identical.

Table 1: Analytical Data of Complexes **1** and **2**

Analytical data	**$[Cu(IBU)_2(H_2O)_2]Cl_2$ Mechanochemical (1a)**	**$[Cu(IBU)_2(H_2O)_2]Cl_2$ Solvent-based (1b)**	**$[Cu(ASP)_2(CH_3COO)_2]$ Mechanochemical (2a)**	**$[Cu(ASP)_2(CH_3COO)_2]$ Solvent-based (2b)**
Colour	Sky- blue	Pale blue	Blue	Bluish green
Conductivity ($\Omega^{-1}mol^{-1}$ cm^2)	102	105	50.3	52.6
R_f	0.58	0.61	0.77	0.82
Yield (%)	96.2	68.9	93.1	62.7
M.pt. (^0C)	122	125	180	182
M.wt. (g/mol)	614.00	614.54	605	604.6
% Cu	10.21	10.21	10.40	10.43
Elemental Analysis	Anal.Calcd (Found) %	Anal.Calcd (Found) %	Anal.Calcd (Found) %	Anal.Calcd (Found) %
	C: 50.81 (50.70)	H: 5.86 (5.67)	N: - -	C: 50.81 (50.60)	H: 5.86 (5.67)	N: - -	C: 43.63 (43.58)	H: 3.63 (3.53)	N: - -	C: 43.63 (44.03)	H: 3.63 (3.54)	N: - -

3.1. FT-IR Spectroscopic Results

Figures 1 and 2 below show a comparison of the FT-IR spectra of the free Ibuprofen and Aspirin ligands with the complexes obtained via mechanochemical (solvent-free) and solvent-based methods (reflux in methanol).

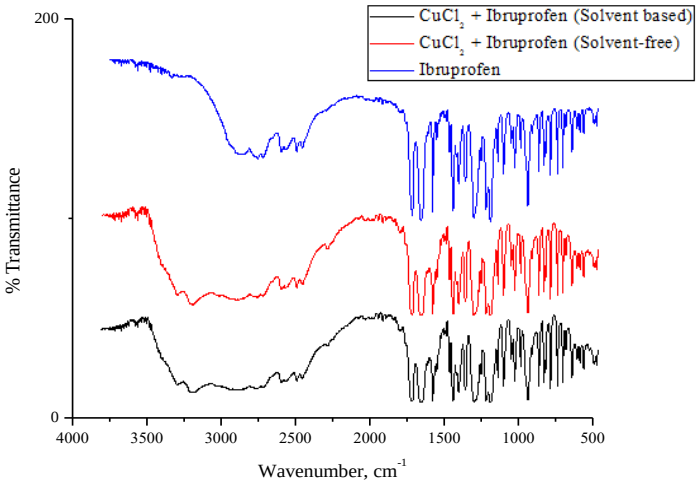


Figure 1: FT-IR spectra for Ibuprofen and its Cu (II) complexes.

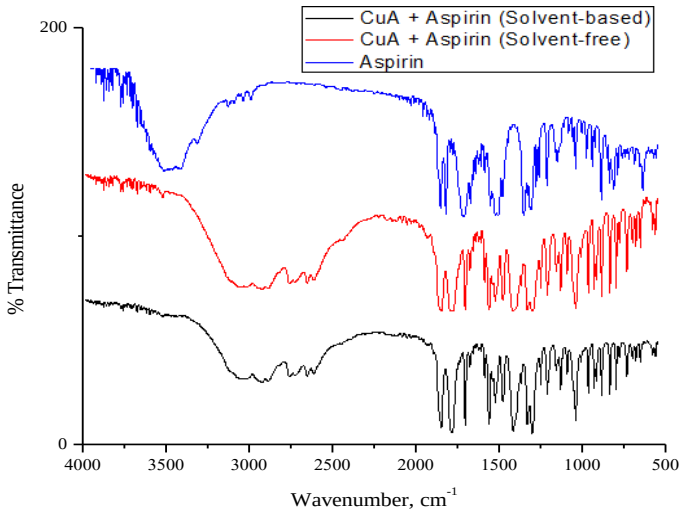


Figure 2: FT-IR spectra of Aspirin and its Cu (II) complexes.

It was illustrated in Figures 1 and 2 that the FT-IR spectra of complexes **1** and **2** synthesized via the two methods are similar, but different from the free ligands (Ibuprofen and Aspirin). Selected FT-IR bands of ibuprofen, aspirin and complexes **1** and **2** with Cu (II) are presented in Table 2 and 3.

Table 2: Selected FT-IR Absorption band (cm^{-1}) for Ibuprofen and its Cu (II) complexes.

S/N	Ligand/Complex	ν O-H	ν C=O	νasCOO	νs COO	ν M-O	νasC-H aliph.	νsC-H arom.	ν Cu-OH_2
1.	**Ibuprofen**	3657s	1753b	1508s	1456b	-	2995b		-
2.	**$[Cu(IBU)_2(H_2O)_2]Cl_2$** Solvent-free-**1a**	3336b, 3446b	1787b	1575b	1419s	599m	2972b	3022b	705b
3.	**$[Cu(IBU)_2(H_2O)_2]Cl_2$** Solvent-based-**1b**	3338b, 3448b	1785m	1579b	1419s	563b	2995b	3022b	704b

Table 3: FT-IR Absorption band (cm^{-1}) for Aspirin and its Cu (II) complexes

S/N	Ligand/Complex	ν O-H	ν C=O	νasCOO	νs COO	νC-O	νM-O	νasC-H aliphatic	νsC-H aromatic	ν Cu-OH
1.	**Aspirin**	3522s 3451s	1772b	1541s	1473b	1093s	-	2995b	3066m	-
2.	**$[Cu(ASP)_2(CH_3COO)_2]$** Solvent-free - **2a**	3489s	1753b	1575s	1419b	1039s	543	2970s, 2999s	-	646b, 667b
3.	**$[Cu(ASP)_2(CH_3COO)_2]$** Solvent-based- **2b**	3489s	1755b	1575s	1419b	1012s,	563	2964s, 2993s	-	646b, 667b

The data presented in Tables 2 and 3 are consistent with the ones reported in literature (Bojidarka, 2007; Kafarska *et al*., 2009; Mariam *et al*, 2010). From the FT-IR data on Table 2, it can be deduced that the carboxylate group takes part in coordination to metal atom. The appearance of new bands in $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ at 1575, 1579 and 1419 cm^{-1} characterizes the nature of the metal-carboxylate bond in both complexes. The difference in the $\Delta\nu$ of $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ stretching values for the complexes **1a** and **1b** which fall in the range 156-187 cm^{-1} showed that the ligand (Ibuprofen) acts as bidentate. The complexation of Cu (II) ion with oxygen - donor ligand is also confirmed by the appearance of ν(M-O) band in the range 563-599 cm^{-1} in both complexes (Abuhijleh, 1997). The appearance of strong absorption band νOH in both complexes around 3336 and 3446 cm^{-1} suggests there is coordination at this site in both complexes.

In addition, the band νM-OH_2 at 705 and 704 cm^{-1} has been attributed to the coordination of Cu (II) ion with water molecules. The shifts/changes in the absorption peaks of $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$, ν(M-O), νC=O (from 1753 to 1787 and 1785cm^{-1}) and νO-H (from 3657 to 3443 and 3446 cm^{-1}) of the free Ibuprofen ligand and its complexes are indications of the formation of a new product through coordination at these sites. Table 3 shows the absorption bands at

3522 and 3451cm^{-1} in the ligand which has been assigned to νO-H group (with prominent peaks). These bands have been shifted to 3489 and 3000 – 2500 cm^{-1} in the broad band of both metal complexes with non-prominent peaks suggesting coordination of this group with Cu(II) ion. In addition, the absorption peak at 1772cm^{-1} due to νC=O group in the ligand has been shifted to 1753 and 1755 cm^{-1} in both complexes with prominent peaks suggesting coordination at this site. The broad band interaction which appeared at 646, 667 and 543 cm^{-1}, 563 cm^{-1} in both Cu(II) complexes have been tentatively assigned to ν(M-OH) and (M-O) modes suggesting the chelation of Cu(II) ion through one oxygen atom of ν(M-OH) and (M-O) groups.

From this study, the stretching band of the asymmetric and symmetric carboxylate groups $\nu_{asym}(COO^-)$ and $\nu_{sym}(COO^-)$ observed at 1575 and 1419 cm^{-1} respectively in both complexes, enhance the deduction that the carboxylate groups took part in coordination to the metal atoms. The difference Δν of $\nu_{asym}COO^-$ and $\nu_{sym}COO^-$ stretching values for the complexes **2a** and **2b** which fall in the range 156 cm^{-1} showed that the ligand acts as bidendate (Chinmay *et al.*, 2008).

3.2 UV-Visible Spectroscopic Result

Tables 4 and 5 below showed that UV-Visible spectra of both complexes synthesized via the two methods are identical. Table 4 shows that the UV-Visible spectrum of free organic ibuprofen ligand in solid-state form presents one absorption band at 292nm, assigned to $\pi \rightarrow \pi^*$ transition. For the complexes **1a** and **1b**, the visible region produced broad band at 547 and 538 nm assigned to d-d transitions ($^2E_g \rightarrow {}^2T_{2g}$), is typical of octahedral symmetry (Sara *et al.*, 2011). In addition, the UV-Visible spectrum (Table 5) of free aspirin ligand in solid-state form presents one absorption band at 292 nm, assigned to $\pi \rightarrow \pi^*$ transition. From this study, the complexes **2a** and **2b** produced broad band at 667 nm typical of $^2E_g \rightarrow {}^2T_{2g}$ (corresponding to d-d transition), and octahedral symmetry. The selected UV-Visible spectral data of Ibuprofen, Aspirin, and complexes **1** and **2** are collected in Tables 4 and 5.

Table 4: Selected UV-Visible Spectroscopic Data of Ibuprofen and its Cu(II) Complexes.

Ligand/Complex	Wavelength (nm)	Energy (cm^{-1})	Absorbance	Assignment
Ibuprofen	292	34247	1.153	$\pi \rightarrow \pi^*$
$[Cu(IBU)_2(H_2O)_2]Cl_2$ Solvent-free-**1a**	547	18282	0.491	$^2E_g \rightarrow {}^2T_{2g}$.
$[Cu(IBU)_2(H_2O)_2]Cl_2$ Solvent-based-**1b**	538	18587	0.373	$^2E_g \rightarrow {}^2T_{2g}$.

Table 5: Selected UV-Visible Spectroscopic Data of Aspirin and its Cu(II) Complexes

Ligand/Complex	Wavelength (nm)	Energy (cm^{-1})	Absorbance	Assignment
Aspirin	292	34246	1.174	$\pi \rightarrow \pi^*$
$[Cu(ASP)_2(CH_3COO)_2]$ Solvent-free-**2a**	667	14993	0.328	$^2E_g \rightarrow {}^2T_{2g}$
$[Cu(ASP)_2(CH_3COO)_2]$ Solvent-based- **2b**	667	14993	0.260	$^2E_g \rightarrow {}^2T_{2g}$

3.3. X-ray Diffraction Studies

Figure 3 below shows a comparison of the X-ray diffraction patterns of $[Cu(ASP)_2(CH_3COO)_2]$ **(2a)** obtained via the solvent-free method and the starting material (Aspirin).

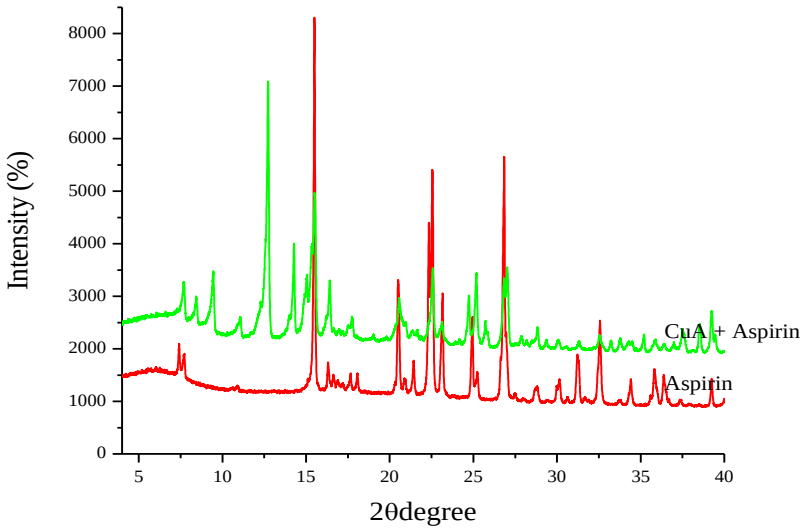


Figure 3: Powder X-ray diffraction patterns of Aspirin and $[Cu(ASP)_2(CH_3COO)_2]$ (2a).

Figure 3 showed that there are new peaks corresponding to the solvent-free product (**2a)** observed at 2θ = 9, 12, 14, and 16^o which were absent in the starting material (Aspirin), indicating the formation of a new phase. This indicates the formation of a new product.

3.4 Proposed Structure of the Cu (II) Complexes

From the Infrared and UV-Visible spectroscopic data coupled with X-ray diffraction studies, the structures of the Cu (II) Complexes of both ibuprofen and aspirin synthesized via solvent-free and solvent-based methods were proposed and shown in Figure 4 and 5 respectively.

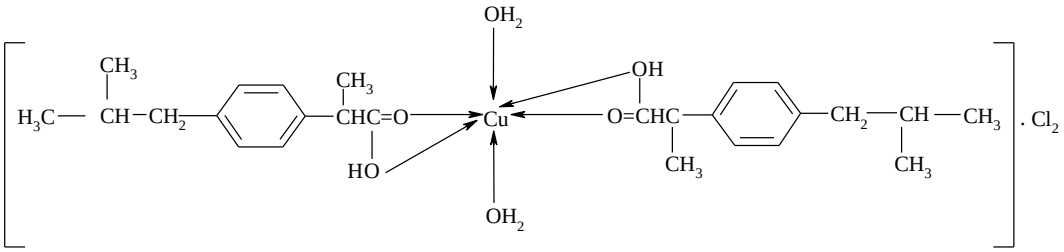


Figure 5: Proposed structure of $[Cu(IBU)_2(H_2O)_2]Cl_2$ complex for both solvent-free and solvent-based products (**1a** and **1b**).

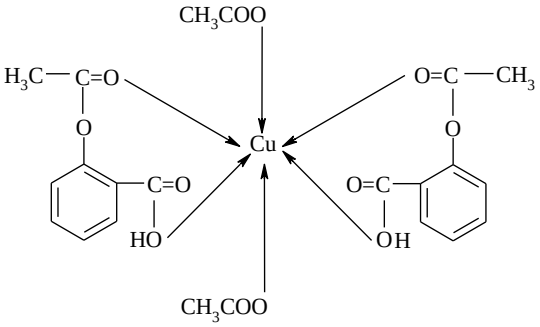


Figure 6: Proposed structure of $[Cu(ASP)_2(CH_3COO)_2]$ complex for both solvent-free and solvent-based products (2a and 2b).

3.5 Antibacterial Activity Studies:

The antibacterial activity of the free ligands and the complexes were recorded at concentrations of 50 and 25 µg/ml using strains of *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia.* Table 6 presents the comparison of antibacterial activity studies on ibuprofen and complexes **1a** and **1b** with Cu (II).

Table 6: Antibacterial activities of Ibuprofen, Aspirin and there Cu (II) complexes.

	E. coli		***S. aureus***		***K. pneumonia***	
	Zone of Inhibition (mm)					
Complex/Ligand	**50µg/ml**	**25µg/ml**	**50µg/ml**	**25µg/ml**	**50µg/ml**	**25µg/ml**
Ibuprofen	5+ 0.43[b]	6+ 0.35[b]	5+ 0.46[b]	6+0.39[c]	4+ 0.5[b]	5+ 0.4[b]
$[Cu(IBU)_2(H_2O)_2]Cl_2$ Solvent-free-**1a**	6+ 0.6[a]	5+ 0.44[b]	7+ 0.5[b]	6+ 0.56[a]	6+ 0.4[b]	5+ 0.48[b]
$[Cu(IBU)_2(H_2O)_2]Cl_2$ Solvent-based-**1b**	5+0.5[b]	6+ 0.55[a]	6+0.53[a]	5+ 0.54[a]	5+0.5[c]	5+ 0.43[c]
Aspirin	8+ 0.63[a]	6+ 0.55[a]	5+ 0.53[a]	3+ 0.32[b]	4+ 0.45[b]	3+ 0.34[b]
$Cu(ASP)_2(CH_3COO)_2]$ Solvent-free-**2a**	7+ 0.44[b]	6+ 0.64[a]	4+ 0.3[b]	5+ 0.33[c]	4+ 0.43[b]	3+ 0.23[c]
$[Cu(ASP)_2(CH_3COO)_2]$ Solvent-based-**2b**	8+0.71[a]	7+ 0.55[a]	4+0.43[b]	4+ 0.3[c]	3+0.23[c]	3+ 0.33[c]

NB: [a]Active (100%); [b]Active (50%); [c]Active (25%) against E. *coli*, S. *aureus and* K.*pneumonia.*

The comparison shows **1a** possesses the highest inhibitory activity against strains of *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumoniae,* isolated from different pathological products at concentrations of 50 and 25 µg/ml in the following order *S. aureus* > *E. coli*> *K. pneumonia.*

Table 6 also presents the comparison of the antibacterial activity of aspirin and complexes **2a** and **2b** with Cu (II).The comparison shows complex **2b** possesses the highest inhibitory activity, than aspirin against strains of *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumoniae,* isolated from different pathological products at concentrations of 50 and 25µg/ml.

4. Conclusion

This study shows remarkable synthesis of Cu (II) complexes of ibuprofen and aspirin via solvent-free and solvent-based methods. It was established that ibuprofen coordinated with copper ion through the oxygen of the carbonyl group, with the ligand acting as bidentate. Two molecules of water are inside the coordination sphere and one molecule of chloride ion is outside the coordination sphere of the complex resulting in an octahedral geometry. On the other hand, aspirin was found to have coordinated with copper ion through the oxygen of the carbonyl group, with the ligand acting as bidentate, forming an octahedral geometry and two

molecules of acetate inside the coordination sphere The antibacterial activity study of the metal-drug complexes **1** and **2** showed that they possess higher inhibitory activity against strains of *E. coli, S. aureus* and *K. pneumoniae* than their parent ligands at concentrations of 50 µg/ml and 25 µg/ml. Comparative study of the two methods used to synthesize $[Cu(IBU)_2(H_2O)_2]Cl_2$ complex (**1),** and $[Cu(ASP)_2(CH_3COO)_2]$ complex (**2)** showed that solvent-free technique was found to be relatively rapid with high yield in comparison to solvent-based synthetic method. Thus, the solvent-free technique was found to be more effective to synthesize the Cu (II) Complexes of ibuprofen and aspirin.

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