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Comparison of Solid and Solvent - Based Syntheses, Characterization and Antioxidant Property of Metal Complexes of Sodium Diclofenac

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Abstract

Mechanosynthesis and solvent – based syntheses of transition metals (Ni, Co and Zn) complexes of Sodium diclofenac has been carried out by 1:1 molar ratio of the ligand to metal salts respectively. The synthesis of the metal complexes were confirmed by melting point determination, FT-IR (Fourier Transform Infra-red) and UV-visible spectroscopies. The ligand showed bidentate coordination to the metal ions through carboxylate moiety. Octahedral geometry was proposed for all the metal complexes. The antioxidant property of metal complexes was determined using DPPH (1,1-diphenyl-2-picrylhydrazyl) assay with Ascorbic acid as control. The antioxidant evaluation results revealed that the synthesized metal complexes are promising antioxidant agents.

Keywords: Mechanosynthesis; DPPH; Carboxylate moiety; antioxidant evaluation

Introduction

Mechanochemistry can be seen as an interface between chemistry and mechanical engineering. Mechanochemistry is radically different from the traditional solvent-based, thermal or photochemical mechanisms because it eliminates the need for many solvents, although, its mechanisms of transformations are often complex (Hickenboth *et al*., 2007; Carlier *et al*., 2013). It involves the synthesis of chemical products by using only mechanical action. For example, grinding and ball milling methods are widely used mechanochemical processes in which mechanical force is used to achieve chemical processing and transformations (Carlier *et al.*, 2011). In recent times, reactions conducted through grinding or milling, rather than solvent mediation, holds great promise for synthetic chemistry. Mechanochemical synthesis is one of the variants of so-called dry technologies, promising to become an economically profitable (due to reduced number of stages) and ecologically clean procedure compared to the traditional processes. It is now emerging as an alternative reaction media to replace solvent-based synthesis since it is environmental-friendly with a substantial good yield, the reactions is rapid, often reaching substantial completion in several minutes compared to hours in organic solvents (Adams & Jonathan, 2009; Tella *et al.*, 2011; Arise *et al*., 2017). This has been widely demonstrated in organic chemistry by Hernández & Friščić (2015),

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in inorganic and coordination chemistry Arise *et al*., 2017; Jobbágy *et al*., 2014) especially in the area of metal organic frameworks {MOFs} (Bisht *et al*., 2015). For example, mechanochemical process has been used as an environmentally preferable way to synthesize pharmaceutically-attractive phenol hydrazones (Oliveira *et al*., 2014).

In present study, sodium diclofenac (Figure. 1) transition metal (Co, Ni, Zn) complexes have been synthesized and monitored by using melting point, Fourier Transform Infra-red (FTIR) and Electronic spectroscopy. The antioxidant property of the synthesized metal complexes was also investigated.

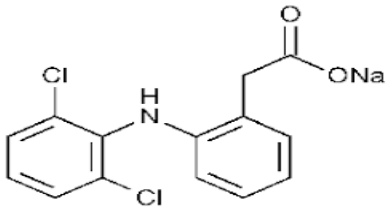


Figure 1: Molecular Structure of Sodium diclofenac (NaD)

Materials and Methods

Materials

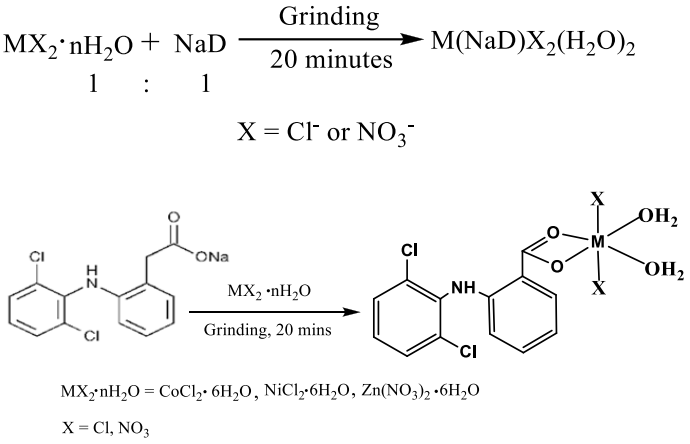
The ligand, Sodium diclofenac (NaD), DPPH and Ascorbic acid were commercially obtained and used without further purification. Hydrated metal salts used for complexation ($NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$ and $Zn(NO_3)_2{\cdot}6H_2O$) were obtained from British Drug House Chemical Limited Co. Poole England.

Instrumentations

Melting points were determined using MPA100 OptiMelt Automated Melting Point system.The FT-IR spectra of both the ligand and the metal complexes were recorded on Thermos Scientific Nicolet i5 Spectrophotometer in the range of 4000 cm^{-1}- 500 cm^{-1} using KBr. Solution electronic absorption spectra of the ligand and complexes were ran in the range of 180 - 400 nm and 180-1100 nm respectively on Jenway 6405 Uv/vis.

Solid state synthesis of NaD-metal complexes

Sodium diclofenac, NaD (1 mmol, 0.3181 g) and each of corresponding metal salts $NiCl_2{\cdot}6H_2O$ (1 mmol, 0.2377 g) ; $Zn(NO_3)_2{\cdot}6H2O$ (1 mmol, 0.2975 g); $CoCl_2{\cdot}6H_2O$ (1 mmol, 0.2379 g) were weighed into a previously washed and dried agate mortar. Using mortar and pestle at room temperature, the metal salts and the ligand were ground continuously for 15 min to a fine paste. The grinding continued for additional 5 minutes until no traces of reactants were left. The powders obtained: Zn (white) , Ni and Co (coloured) were washed with little methanol to remove unreacted starting materials . Fine powders obtained in each case as product were weighed and dried in a dessicator over silica gel.



Scheme 1: **Solid state synthesis of NaD-metal complexes**

$Co(NaD)Cl_2(H_2O)_2$: Yield: 0.5245 g (90.4%) ; M. wt : 461.01 g/mol ; M. pt :179 – 182°C; FTIR (KBR, cm^{-1}): 3551, 3324, 1694, 1626,1479, 1413, 1322, 1282, 1199, 766, 741, 629, 609, 529; UV-Vis(DMSO) λ, nm: 282, 454, 688, 884

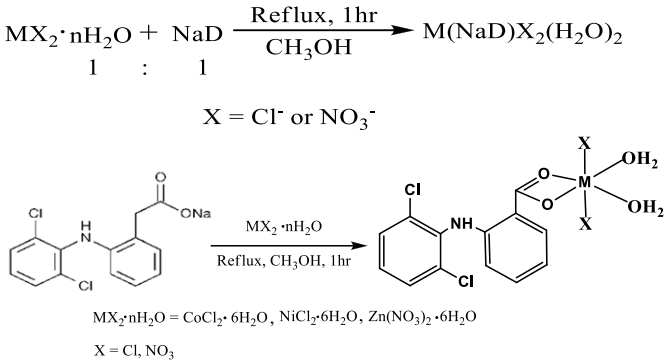
$Ni(NaD)Cl_2(H_2O)_2$: Yield: 0.4533 g (89.3%) ; M. wt : 460.77 g/mol ; M. pt : 195°C; FTIR (KBR, cm^{-1}): 3422, 1694, 1621, 1283, 766, 742, 530, 452 ; UV-Vis(DMSO) λ, nm: 224, 296, 570, 640, 753

$Zn(NaD)(NO_3)_2(H_2O)_2$: Yield: 0.5339 g (92.6%) ; M. wt : 520.95 g/mol, M. pt : 213°C; FTIR (KBR, cm^{-1}): 3751, 3456, 1628, 1509, 1381, 1295, 1250, 1168, 766, 746, 636, 560, 532, 484, 453; UV-Vis(DMSO) λ, nm: 226, 290

Solvent-based synthesis of NaD-metal complexes

A solution of Sodium Diclofenac (1 mmol, 0.3181 g) in methanol (10 mL) was drop-wisely added to each of solution of $NiCl_2{\cdot}6H_2O$ (1 mmol, 0.2377 g) ; $Zn(NO_3)_2{\cdot}6H_2O$ (1 mmol, 0.2975 g); $CoCl_2{\cdot}6H_2O$ (1 mmol, 0.2379 g) in methanol (10

mL). The resulting solutions were refluxed for 1 hour at 70˚C. There were colour changes during the course of refluxing. The precipitates formed after the solution was gently evaporated and the concentrate was allowed to cool for 30 minutes at room temperature. The precipitates were filtered, washed (3 times) with methanol and dried over silica gel in the dessicator.



Scheme 2: Solvent-based synthesis of NaD-metal complexes

$Co(NaD)Cl_2(H_2O)_2$: Yield: 0.2245 g (60.7%) ; M. wt :461.01 g/mol ; M. pt : 178 – 180˚C; FTIR (KBR, cm^{-1}): 3553, 3321, 1695, 1626,1480, 1412, 1322, 1281, 1199, 766, 741, 629, 609, 527; UV-Vis(DMSO) λ, nm: 282, 452, 680, 887.

$Ni(NaD)Cl_2(H_2O)_2$: Yield: 0.1533 g (58.3%) ; M. wt : 460.77 g/mol ; M. pt : 197˚C; FTIR (KBR, cm^{-1}): 3424, 1691, 1619, 1281, 766, 742, 530, 450 ; UV-Vis(DMSO) λ, nm: 224, 295, 570, 642, 751.

$Zn(NaD)(NO_3)_2(H_2O)_2$: Yield: 0.3327 g (75.6%) ; M. wt : 520.95 g/mol, M. pt : 214˚C; FTIR (KBR, cm^{-1}): 3751, 3454, 1626, 1507, 1381, 1295, 1250, 1166, 766, 746, 636, 560, 531, 484, 450; UV-Vis(DMSO) λ, nm: 224, 292.

Evaluation of antioxidant activities of Metal (II) Complexes

DPPH Antioxidant Assay

The determination of the free radical scavenging activity of the metal complexes was carried using the DPPH (1,1-diphenyl-2-picrylhydrazyl) assay. Appropriate dilution of the metal complexes (1 ml) was mixed with 3 ml of 60µM acetone, acetic anhydride, DMSO, solution of DPPH radicals; the mixture was left in the dark for 30 min before the absorbance was measured at 517 nm. The decrease in absorbance of $DPPH^{\cdot}$ on addition of test samples relative to the control (ascorbic acid) was used to calculate the percentage inhibition (% Inhibition) according to the following the equation:

$$\% \text{ Inhibition} = [(Abs_{control} - Abs_{sample}) \div Abs_{control}] \times 100.$$

Results and Discussion

The mechanochemical method (Scheme 1) was carried out by manual grinding of Sodium diclofenac and hydrated metal salts of cobalt, nickel and zinc using mortar and pestle. The reaction was done within 20 minutes at room temperature with greater yield as compared to solvent-based (Scheme 2) reaction (120 min in methanol at 70˚C) and 3 days for products to form. The melting point of the metal complexes differ from that of the NaD (288 - 290˚C): this gives an insight into the formation of the coordination compounds. Also, the high purity of the complexes can be predicted from their sharp melting point.

The colours of cobalt (deep purple) and nickel (pale green) complexes are distinctly different from that of the ligand (white). Thus, it can be inferred that the colours displayed by the metal complexes are determined by the metal ions, a possible indication to the formation of coordination compounds.

The metal complexes were completely soluble in polar solvents such as water and methanol and also in DMF and DMSO but, practically insoluble in non-polar solvents indicating that the metal complexes are polar in nature and have tendencies to conduct electricity in solution.

FTIR: The characteristics absorption bands in the spectra of ligands and metal complexes are shown in Table 1. The FT-IR spectra of the complexes synthesized via the two methods are identical, but different from the free ligand (sodium diclofenac, NaD), suggesting that both methods produced similar products.

The FTIR spectrum of sodium diclofenac (Figure 2) showed a broad absorption band at 3411 cm^{-1} which is assignable to the stretching frequency of OH/ONa of carboxylic acid group. This band undergone shift in the spectra of the metal complexes (Figure 3 - 5) which is a possible indication that sodium diclofenac coordinated to the metal ions through oxygen atom of hydroxyl

group of carboxylic acid through replacement of sodium atom by metal ions. This is further supported by the stretching frequency of C-O which was observed at 1295 cm^{-1} in the spectrum of sodium diclofenac and shifted bathochromically in the spectra of metal complexes. This confirms the participation of oxygen in the C-O-M bond (Sharma *et al*., 2011; Osunniran *et al*., 2018).

The band observed at 1604 cm^{-1} and 1471 cm^{-1} in the spectrum of sodium diclofenac assigned to the asymmetric and symmetric stretching frequency of C=O shifted in all the spectra of metal complexes equally supported the proof of coordination of sodium diclofenac to the metal ions through Carboxylate moiety (Obaleye *et al*., 2014). The absorption bands between 3751 cm^{-1} and 3550 cm^{-1} were assigned to stretching frequency of H_2O molecule coordinated to the metal ions. The strong bands in the range of 1480 – 1590 cm^{-1} were assigned to aromatic benzene stretching frequency. The bands found between 450 cm^{-1} and 532 cm^{-1} at the fingerprint region of the spectra of the metal complexes is attributed stretching frequencies of M-N, M-O and M-Cl. These revealed the metal-ligand coordination (Obaleye *et al.,* 2014; Osunniran *et al*., 2018).

Table 1: Selected FT-IR absorption band (cm^{-1}) for ligand and Metal Complexes

Ligand/Complexes	υ(ONa)/ υ (OH)	υ (COO) (asy, sym)	υ (C-O)	υ(H_2O)	υ(M-O/M-X)
NaD	3411	1604, 1471	1291	---	----
$Co(NaD)Cl_2(H_2O)_2$ Mechanochemical	3324	1654, 1587	1282	3551	529
$Co(NaD)Cl_2(H_2O)_2$ Solvent – based	3326	1654, 1587	1281	3550	527
$Ni(NaD)Cl_2(H_2O)_2$ Mechanochemical	3422	1621, 1588	1283	3654	530,452
$Ni(NaD)Cl_2(H_2O)_2$ Solvent – based	3421	1620, 1586	1281	3653	530,450
$Zn(NaD)(NO_3)_2(H_2O)_2$ Mechanochemical	3456	1628, 1579	1250	3751	532,484,453
$Zn(NaD)(NO_3)_2(H_2O)_2$ Solvent – based	3458	1626, 1579	1250	3751	531,484,450

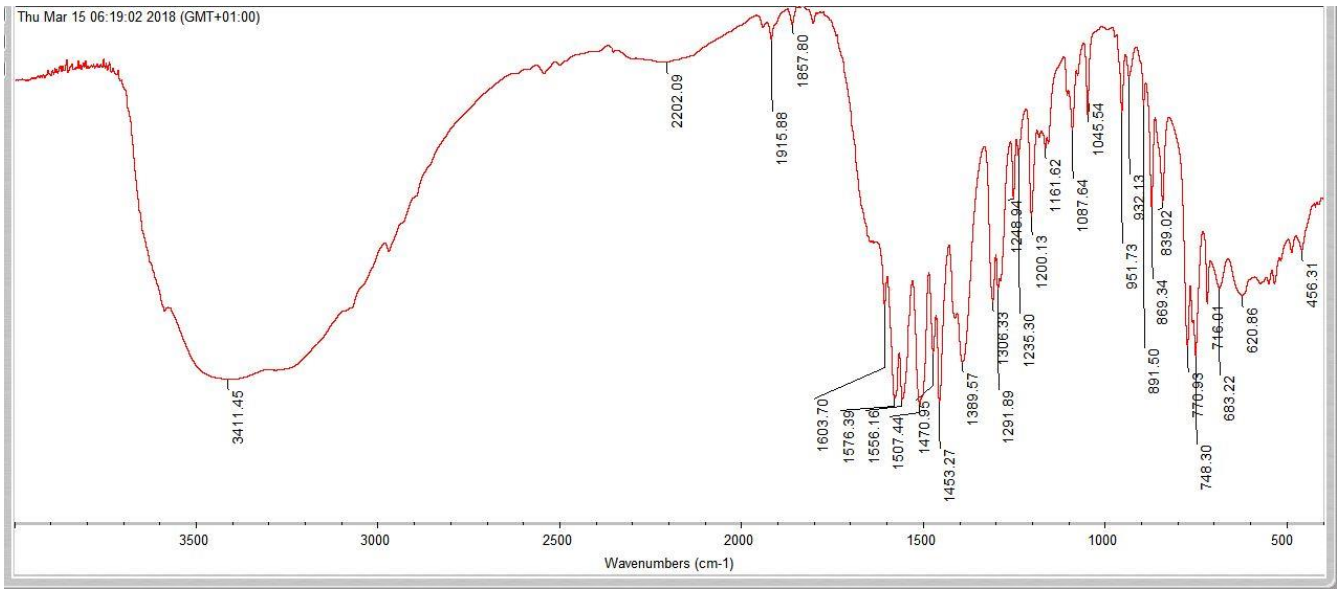


Figure 2: FTIR spectrum of sodium diclfenac (NaD)

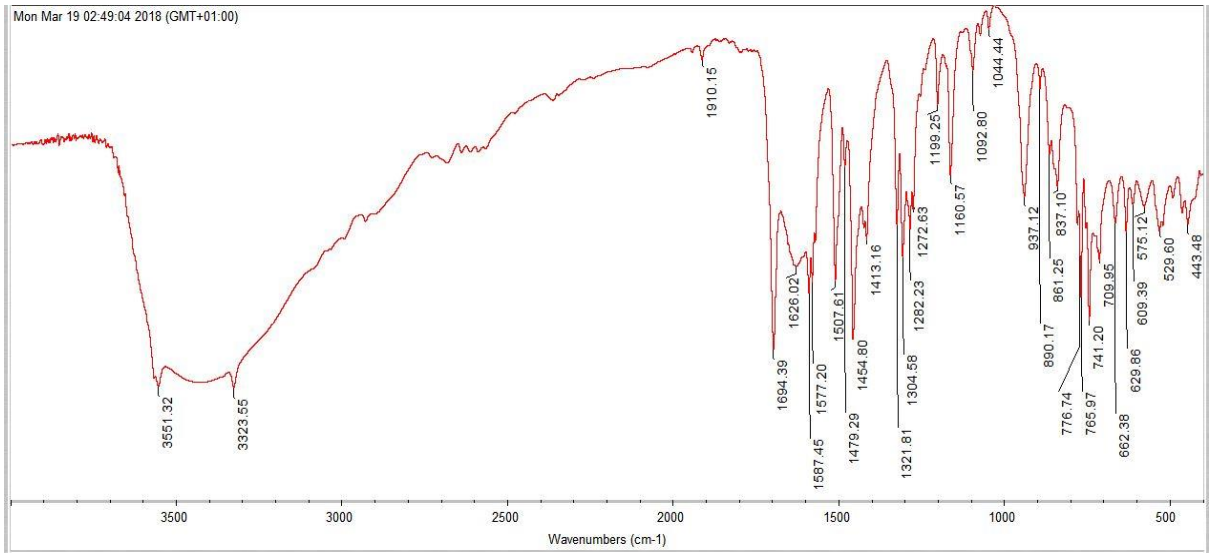


Figure 3: FTIR spectrum of $CoNaDCl_2(H_2O)_2$

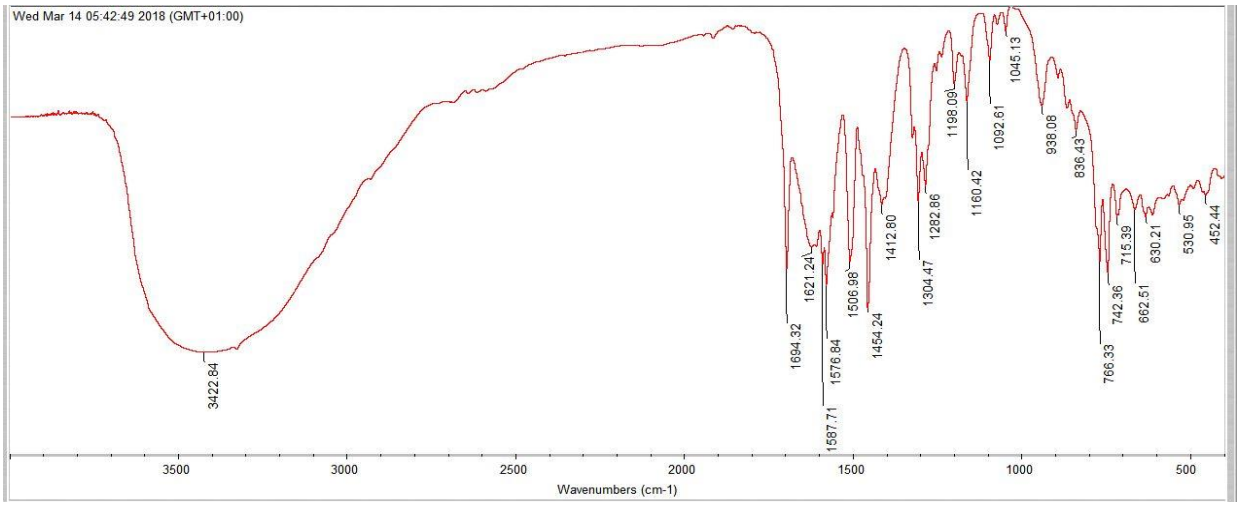


Figure 4: FTIR spectrum of $NiNaDCl_2(H_2O)_2$

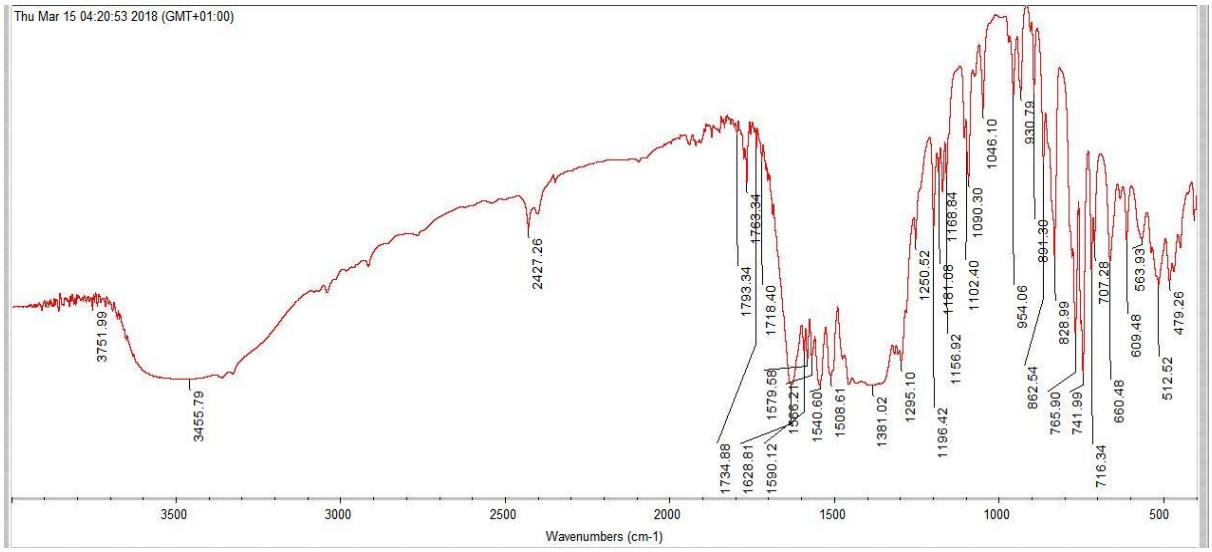


Figure 5: FTIR spectrum of $ZnNaD(NO_3)_2(H_2O)_2$

Electronic spectra: The electronic spectra data of ligand and metal complexes is contained in Table 2.The electronic spectrum of the free ligand in DMSO showed absorption bands in the UV-region at 196 nm and 246 nm. These bands are assigned to intra-ligand transition due to n-π* transition of the non-bonding electrons present on the oxygen of (C=O) group. The slight shift and disappearance of the bands in the spectrum of metal complexes relative to the ligand is attributable to coordination (Obaleye *et al.,* 1997). The absorption spectra of Co (II) and Ni (II) complexes of NaD showed three bands in the visible region corresponding to the electronic transitions for d^7 and d^8ion respectively in an octahedral environment (Najeeb, 2018; Osunniran *et al.,*2018). Zn(II) compounds do not have additional bands in the visible region since it has d^{10} configuration and as such there is no d-d transition. However, hypsochromic shifts of the first and second bands points to complex formation (Ali & Jabali, 2016; Osunniran *et al.,* 2018).

Antioxidant Activity

The IC_{50}, which stands for the concentration of fraction required for 50% scavenging activity, was calculated from the dose-inhibition linear regression equation of each complex. The antioxidant property of metal complexes is determined by comparing their IC_{50} with that of ascorbic acid. The result of antioxidant evaluation of the synthesized metal complexes (Figure 6 (a-d)) revealed that the IC_{50} of $Co(NaD)Cl_2(H_2O)_2$, $Ni(NaD)_2Cl_2(H_2O)_2$, and $Zn(NaD)(NO_3)_2(H_2O)_2$ is lower than that of ascorbic acid and as such they possess a very good antioxidant property.

Conclusion

Mechanochemical synthesis of sodium diclofenac – metal complexes represents a comparatively best method of synthesis with no environmental pollution, economically profitable, appreciably good yield and rapid when compared to the solvent-based synthesis that leads to environmental pollution and takes a longer period of time. Coordination compounds of cobalt, nickel and zinc containing sodium diclofenac as ligand have been synthesized by solvent-free and solvent-based methods, and characterized by FT-IR, UV-visible techniques and melting point determination. The ligand was found to behave as bidentate ligand coordinated to the metal ions through Carboxylate. Octahedral geometry was proposed for all the metal complexes based on spectroscopic results. Antioxidant evaluation of the metal complexes carried out revealed that the synthesized metal complexes are promising antioxidant agents

Table 2: Electronic Spectra data of the Ligand and the Metal complexes

	λ_{max} (nm)	λ_{max} (cm^{-1})	λ_{max} Energy ($KJmol^{-1}$)	Assignment
NaD	196	51,020	610	n – π*
	246	40,650	486	n – π*
$Co(NaD)Cl_2(H_2O)_2$	282	35,461	424	n – π*
	454	22,026	263	$^4T_{1g}(F) \longrightarrow {}^4T_{1g}(P)$
	688	14,535	174	$^4T_{1g}(F) \longrightarrow {}^4A_{2g}(F)$
	884	11,312	135	$^4T_{1g}(F) \longrightarrow {}^4T_{2g}(F)$
$Ni(NaD)Cl_2(H_2O)_2$	224	44,643	534	n – π*
	296	33,784	404	n – π*
	570	17,544	210	$^3A_{2g}(F) \longrightarrow {}^3T_{1g}(P)$
	640	15,652	187	$^3A_{2g}(F) \longrightarrow {}^3T_{1g}(F)$
	753	13,280	159	$^3A_{2g}(F) \longrightarrow {}^3T_{2g}(F)$
$Zn(NaD)(NO_3)_2(H_2O)_2$	226	44,248	530	n – π*
	290	34,483	412	n – π*

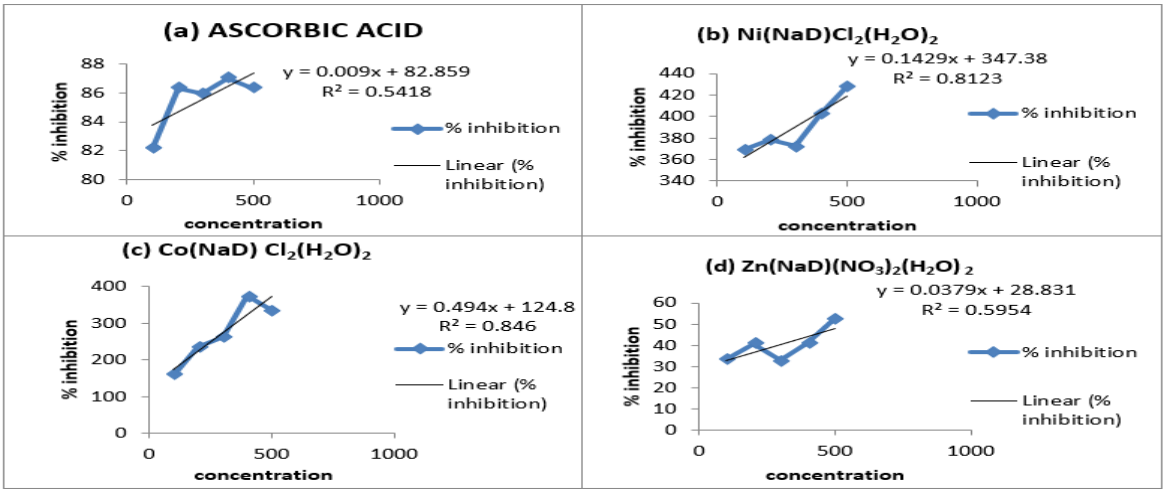


Figure 6: % inhibition versus concentration curve of (a) Ascorbic acid (b) $Ni(NaD)Cl_2(H_2O)_2$ (c) $Co(NaD)\ Cl_2(H_2O)_2$ (d) $Zn(NaD)(NO_3)_2(H_2O)_2$

Supporting Information: FTIR spectra of ligand and the metal complexes.

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