



ORIGINAL ARTICLE

# Solvent-free mechanochemical synthesis and X-ray studies of Cu(II) and Ni(II) complexes of 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine (Trimethoprim) in a ball-mill



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## KEYWORDS

Solvent-free synthesis;  
Trimethoprim;  
X-ray diffraction pattern;  
Mechanochemistry;  
Green chemistry

**Abstract** Solvent-free synthesis of  $[\text{Cu}(\text{CH}_3\text{COO})_2(\text{TMP})_2](\mathbf{1})$  and  $[\text{Ni}(\text{CH}_3\text{COO})_2(\text{TMP})_2](\mathbf{2})$  by ball milling of  $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$  and  $\text{Ni}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$  with Trimethoprim in the absence of solvent is described. Conventional synthesis of **1**.  $\text{CH}_3\text{OH}$  and **2**.  $\text{CH}_3\text{OH}$  was carried out by the reaction of metal acetate salt and Trimethoprim using the solution-based method (reflux in  $\text{CH}_3\text{OH}$  for 2 h) for comparison purposes.

The mechanochemical products were characterized by comparison of melting points, conductivity values, spectral data, XRPD patterns with those of free ligand and solution based conventional synthesis products.

X-ray diffraction patterns of the complex were similar to the simulated pattern of the complex obtained from single crystal structure suggesting the formation of identical compounds as obtained in solvent medium. The process presented here is operationally simple, environmentally benign and affords excellent yields without the need for solvents or external heating. Clearly, it can present a higher efficiency in terms of materials, energy and time compared to classical solution phase synthesis.

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## 1. Introduction

Environmental concerns provide a compelling incentive to develop chemical reactions that minimize waste productions

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(Tanaka, 2003). The main basis for this interest is the potential reduction in environmental contamination and the increased convenience associated with the elimination of solvent from synthesis reactions (Garay et al., 2007; Cave et al., 2001). The development of solvent-free (or solventless) reaction is an especially attractive goal in the context of green chemistry. Now, chemists all over the world are finding new ways to carry out their reactions more efficiently, with less waste and without using volatile, flammable, toxic and environmentally malign organic solvents. Solvent-based synthesis involves the use of solid reactants, the solvent plays the important role of allowing the reactant molecules to come into close contact with each

other so that they can interact to form a product. In the absence of a solvent, the same result can sometimes be achieved by grinding the solid reactants together (mechanochemistry) and this has been used as a solvent free synthetic method for the preparation of a variety of metal complexes (Braga et al., 2005, 2008, 2009; Tella et al., 2011, 2012; Tella and Obaleye, 2010; Balema et al., 2005; Ernest et al., 2010). The use of coordination complexes of active pharmaceutical ingredients (API) may open up new routes to the delivery of drugs at the biological level because of foreseeable differences in stability, solubility and bioavailability of the free drug with respect to coordinated drug. A surprising aspect of these studies is that, in some cases, the reaction is faster than the corresponding solvent based reaction.

Primarily, the interest in solvent-free conditions stem from the possibility of both solvent based and non-solvent technique giving rise to the same product. The process is cheaper, less time consuming and often more environmentally friendly (Toda, et al., 1990; Desiraju, 1995). The mechanochemical method ranges from simply grinding reactants with mortar and pestle to ball-milling process (Kaupp, 2006; Mashkouri and Naima-Jaimal, 2009). Ball-milling is a mechanochemical technique that is widely applied to the grinding of minerals into fine particles for the preparation and modification of inorganic solids (Ren et al., 2003). Ball-milling is of interest because it is performed in the absence of solvent, under environmentally friendly condition. When two solids are ground together, the heat generated in the grinding process may be sufficient to either create a melt at the surface or completely melt the solid reagents. This could arise from the generation of a "hot spot" (an exotherm) that could lead to a self-sustaining reaction. From a thermodynamic view point, the chemical potential of a substance in the solid state is greater than that for the same substance in the liquid state or in solution, so the driving force for the reaction should be greater than that for a solvent-based synthesis (Atkins, 2006). The first solvent-free synthesis of metal–drug complexes was reported by Braga et al., 2008. Zinc and copper complexes of neuroleptic drug gabapentin were synthesized by Braga and co-workers by simple grinding of solid gabapentin and the inorganic salts of  $ZnCl_2 \cdot 2H_2O$  and  $CuCl_2 \cdot 2H_2O$ . Recently, our group reported the solvent-free synthesis of Co(II) and Ni(II) cimetidine complexes (Tella et al., 2011). The compounds were obtained in high yields in a shorter time of 15 min as compared to the traditional solvent-based synthesis which required volatile organic compounds and many hours of preparation. Trimethoprim is a bacteriostatic antibiotic mainly used in the prophylaxis and treatment of urinary tract infection. It belongs to the chemotherapeutic class of drug known as dihydrofolate reductase inhibitor (Rang et al., 1999).

Metal complexes of Trimethoprim are reported in the literature (Demartzi-kovala and Tsangans, 1986; Zorroddu et al., 1987; Simo et al., 2000; Tella and Obaleye, 2010). Most of these complexes have been synthesized by the traditional method using volatile organic compounds (VOCs) as solvents. As part of our programmes to synthesize metal complexes of active pharmaceutical ingredients in the absence of solvent, we now wish to report a facile environmentally friendly and clean synthesis of Cu(II) and Ni(II) complexes of Trimethoprim using a ball-mill in the absence of solvent. The present paper describes some studies that were carried out to further explore the applicability of such methods to metal complex formation. To the

best of our knowledge, mechanochemical solvent-free synthesis of 5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine(Trimethoprim) complexes has not been reported in the literature.

## 2. Experimental

### 2.1. Materials and instrumentation

All reagents and chemicals were of analytical grade and used as obtained from Aldrich. Trimethoprim was obtained as gift from Sam Pharmaceutical Ltd, Ilorin, Nigeria. Metal salts used include nickel acetate  $[Ni(CH_3COO)_2 \cdot 4H_2O]$ , copper acetate  $(Cu(CH_3COO)_2 \cdot H_2O)$ , infra-red spectra were obtained from samples in the form of KBr pellets using a Perkin Elmer FTIR spectrometer. Metal analyses were carried out by atomic absorption spectroscopy with a Perkin Elmer Spectrometer, model 3110. UV–Vis spectra were obtained on an Aquamate V4.60 spectrophotometer. The analyses of carbon, hydrogen and nitrogen were carried out on a Perkin Elmer 204C micro-analyser. Powder XRD analysis was performed on a Syntag PADS diffractometer at 294 K using Cu  $K\alpha$  radiation ( $\lambda = 1.54059 \text{ \AA}$ ) obtained at Queen's University Belfast, United Kingdom. Ball-mill apparatus was a RetchMM2000. Magnetic susceptibility measurements of the complexes were determined at room temperature by the Gouy method. Mercury tetrathiocyanatocobaltate(II)  $Hg[Co(NCS)_4]$  was used as calibrant.

## 3. Synthesis of the complex

### 3.1. Synthesis of $[Cu(OOCCH_3)_2(TMP)_2]$

#### (a) Mechanochemical synthesis

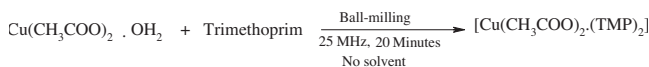
Copper acetate  $[Cu(CH_3COO)_2 \cdot H_2O]$  (0.199 g, 1.0 mmol) and Trimethoprim (0.580 g, 2.0 mmol) were carefully weighed into a Retsch MM200 stainless steel ball-mill vessel equipped with steel balls (20 g), the vessel was closed and the milling was carried out at room temperature at a speed of 25 HZ. After every 5 min milling cycles, the progress of the reaction was monitored by Thin layer chromatography. The milling continued for 20 min overall using TLC to monitor the reaction till no traces of reactants were found. The equation of the reaction is shown in Scheme 1.

Yield 80%, M.wt = 761 M.pt = 185 °C, Anal. Calcd. for  $[C_{32}H_{42}N_8O_{10}Cu]$ ; C, 50.46; H, 5.51; N, 14.72; Cu, 8.28. Found: C, 50.21; H, 5.18; N, 14.67; Cu, 8.13. IR (KBr,  $cm^{-1}$ ): 3553, 3449, 3365, 3256, 3156, 1640, 1585, 1498, 1379, 1245, 1126, 981, 880, 676, 600, 549. UV–Vis (DMSO)  $\lambda$ , nm: 268, 767.

### 3.2. Synthesis of $[Cu(OOCCH_3)_2(TMP)_2] \cdot CH_3OH$

#### (b) Conventional/solvent-based synthesis

Trimethoprim (0.586 g, 2.0 mmol) was dissolved in 30 ml of methanol followed by slow addition of  $Cu(CH_3COO)_2 \cdot H_2O$



**Scheme 1** Mechanochemical synthesis of  $[Cu(OOCCH_3)_2(TMP)_2]$  in a ball-mill.

(0.203 g, 1 mmol) in 50 ml of methanol. The resulting green solution was refluxed for 2 h. The solution was left to evaporate slowly at room temperature. Green crystals formed after 5 days. The equation of the reaction is shown in Scheme 2.

Yield 64%, M.wt = 796, M.pt = 188 °C Anal. Calcd. for  $[\text{C}_{33}\text{H}_{46}\text{N}_8\text{O}_{11}\text{Cu}]$ : C, 49.75; H, 5.78; N, 14.07; Cu, 7.91. Found: C, 48.67; H, 5.46; N, 14.60; Cu, 8.01. IR (KBr,  $\text{cm}^{-1}$ ) 3553, 3449, 3365, 3256, 3156, 1640, 1585, 1498, 1379, 1245, 1126, 981, 880, 676, 600, 549. UV-Vis (DMSO)  $\lambda$ , nm: 272, 774.

### 3.3. Synthesis of $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2]$

#### (a) Mechanochemical synthesis

Nickel acetate ( $\text{Ni}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$ ) (0.249 g, 1.0 mmol) and Trimethoprim (0.586 g, 2.0 mmol) were carefully weighed into a Retsch MM200 stainless steel ball-mill vessel equipped with steel balls (20 g), the vessel was closed and the milling was carried out at room temperature at a speed of 25 Hz. After every 5 min milling cycles, the progress of the reaction was monitored by thin layer chromatography. The milling continued for 20 min overall using TLC to monitor the reaction till no traces of reactants were found. The equation of the reaction is shown in Scheme 3.

Yield 87%, M.wt = 757, M.pt = 98 °C Anal. Calcd. for  $[\text{C}_{32}\text{H}_{42}\text{N}_8\text{O}_{10}\text{Ni}]$ : C, 50.74; H, 5.55; N, 14.80; Ni, 7.70. Found: C, 50.56; H, 5.13; N, 14.00; Ni, 8.00. IR (KBr,  $\text{cm}^{-1}$ ): 3461, 3369, 3182, 2938, 1631, 1590, 1564, 1505, 1472, 1421, 1331, 1236, 1125, 1000, 781, 739, 665, 529. UV-Vis (DMSO)  $\lambda$ , nm: 432, 556, 785.

### 3.4. Synthesis of $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$

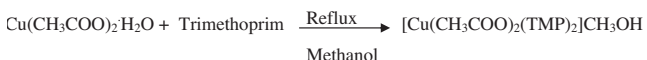
#### (b) Conventional/solvent-based synthesis

Trimethoprim (0.586 g, 2.0 mmol) was dissolved in 30 ml of methanol followed by slow addition of  $\text{Ni}(\text{CH}_3\text{COO})_2 \cdot 4\text{H}_2\text{O}$  (0.249 g, 1 mmol) in 50 ml of methanol. The resulting green solution was refluxed for 2 h. The solution was left to evaporate slowly at room temperature. Green crystals formed after 5 days. The equation of the reaction is shown in scheme 4.

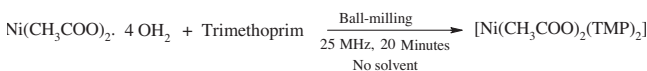
Yield 58%, M.wt = 789, M.pt = 102 °C. Anal. Calcd. for  $[\text{C}_{34}\text{H}_{50}\text{N}_8\text{O}_{12}\text{Ni}]$ : C, 50.19; H, 5.83; N, 14.20; Ni, 7.44. Found: C, 49.56; H, 5.94; N, 13.64; Ni, 7.22. IR (KBr,  $\text{cm}^{-1}$ ) 3470, 3353, 3216, 2939, 1631, 1592, 1562, 1507, 1422, 1332, 1238, 1126, 1003, 781, 675, 529. UV-Vis (DMSO)  $\lambda$ , nm: 410, 570, 700.

## 4. Results and discussion

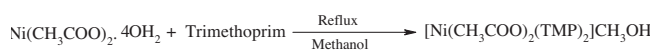
The mechanochemical synthesis of  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$ (1) and  $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2]$ (2) was achieved by grinding metal



**Scheme 2** Solvent-based synthesis of  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$ .



**Scheme 3** Mechanochemical synthesis of  $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2]$  in a ball-mill.



**Scheme 4** Solvent-based synthesis of  $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$ .

acetate salt and Trimethoprim in a ball-mill for 20 min at a frequency of 25 Hz. The product was obtained in high yield. The reaction was monitored by thin layer chromatography using a sample of the powder taken every 5 min. Conventional synthesis of 1. $\text{CH}_3\text{OH}$  and 2. $\text{CH}_3\text{OH}$  was carried out by the reaction of metal acetate salt and Trimethoprim using the solution-based method (reflux in  $\text{CH}_3\text{OH}$  for 2 h) to obtain 1. $\text{CH}_3\text{OH}$  and 2. $\text{CH}_3\text{OH}$ . The crystal structure of  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$  has also been reported in the literature (Naldini et al., 1984) and shown to consist of octahedral complexes. The analytical data of trimethoprim and its metal complexes synthesized by both methods are shown in Table 1.

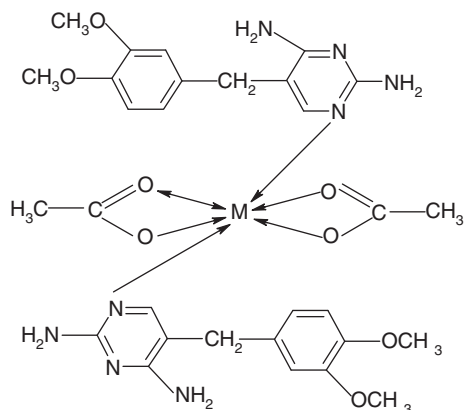
The solid state reaction (Mechanochemical method) was completed within a shorter time of 20 min as compared to conventional synthesis solution method which usually takes 2 h for refluxing and 5 days to get the product. No solvent and heat are used during the mechanochemical synthesis. It was carried out at room temperature. The products were generally obtained with no waste and no further tremendous purification processes were required. The analytical data of Cu(II) and Ni(II) Trimethoprim complexes prepared via the two different methods described above are identical. The mechanochemical products were characterized by comparison of spectral data, XRPD patterns, elemental analysis and melting points with those of free ligand and solution based products. Comparison of solubilities, conductivities and melting points of the samples synthesized via the two methods show that there is no difference in their values. All the products are soluble in methanol, ethanol, and DMSO but insoluble in non-polar organic solvents. The complexes are non-hygroscopic solids with melting points higher than the ligand. The compounds were found to be non-electrolytes since they have low conductivity values. All these results are in good agreement with data obtained from the synthesis of metal complexes of trimethoprim in solvent medium (Demartzi-kovala and Tsangans, 1986; Zorroddu et al., 1987; Simo et al., 2000; Tella and Obaleye, 2010). Trimethoprim possesses seven potential donor sites, two pyrimidinyl N atoms, two  $\text{NH}_2$  groups on the pyrimidine rings and three methoxyl groups. But in all the complexes synthesized using mechanochemical and conventional solution based techniques, Trimethoprim acts as a monodentate ligand that binds through pyrimidine N(1) with metal atoms. Both the copper and nickel atoms are in a distorted octahedral environment in which each is bonded to trimethoprim, through pyrimidinic nitrogen, N(1) position and two bridging acetate ligands as shown in Figs. 1 and 2.

#### 4.1. Infrared spectroscopy

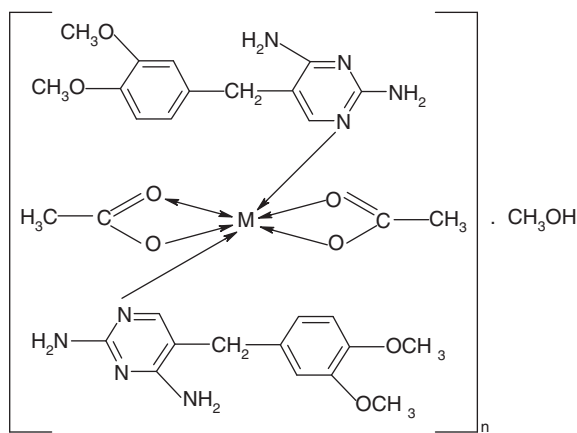
The Infra-red spectra of the products from mechanochemical and solvent-based methods are compared with Trimethoprim ligand. Fig. 3 shows the IR spectra of Trimethoprim as compared with  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$ [1] and 1. $\text{CH}_3\text{OH}$  while Fig. 4 shows infra-red spectra of Trimethoprim as compared with  $[\text{Ni}(\text{OOCCH}_3)_2(\text{TMP})_2]$ (2) and 2. $\text{CH}_3\text{OH}$ .

It can be observed from the spectra that the N-H stretching frequencies of the pyrimidine  $\text{NH}_2$  in the free Trimethoprim

S/N	Complex/ligand	Colour	Method	M.wt.	Melting point (°C)	% Yield	Conductivity
1	TMP	—	—	—	198	—	0.2
2	[Cu(COOCH <sub>3</sub> ) <sub>2</sub> (TMP) <sub>2</sub> ] <sub>1</sub>	Light green	Mechanochemical	761	185	80	7.0
3	1. CH <sub>3</sub> OH	Green	Solution-based	796	188	64	7.6
4	[Ni(COOCH <sub>3</sub> ) <sub>2</sub> (TMP) <sub>2</sub> ] <sub>2</sub>	Green	Mechanochemical	757	98	87	8.6
5	2. CH <sub>3</sub> OH	Green	Solution-based	789	102	58	8.0

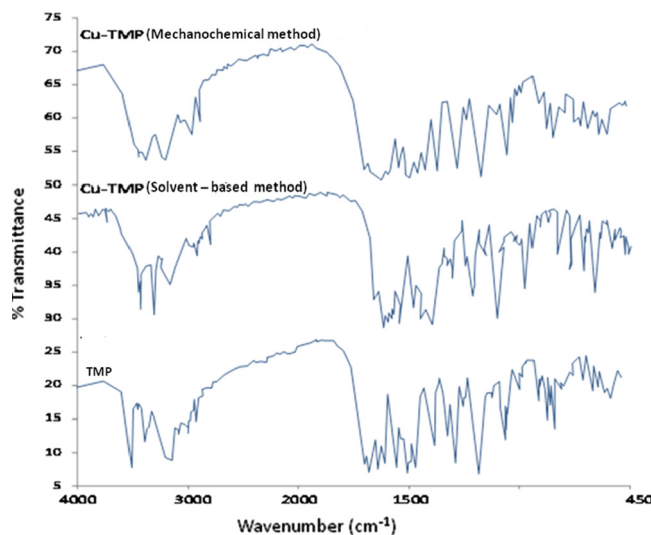


**Figure 1** Proposed structure of [M(CH<sub>3</sub>COO)<sub>2</sub>(TMP)<sub>2</sub>] synthesized by mechanochemical method. M=Cu or Ni.



**Figure 2** Proposed structure of [M(CH<sub>3</sub>COO)<sub>2</sub>(TMP)<sub>2</sub>]<sub>n</sub>·CH<sub>3</sub>OH synthesized by conventional/solvent based method. M=Cu or Ni.

assigned at 3470 and 3318 cm<sup>-1</sup> are affected by H-bonding as shown by a broad band at 3122 cm<sup>-1</sup>. In all the complexes of 1, 2, 1.CH<sub>3</sub>OH and 2.CH<sub>3</sub>OH synthesized both by mechanochemical and solution based methods, these bands due to symmetrical and asymmetrical modes of NH<sub>2</sub> spectra are not significantly shifted in the complexes (Weissberger, 1956; Cotton, 1960; Nakamoto, 1963; Rao, 1963; Bellamy, 1964). The little shift may be due to hydrogen bonding as previously reported (Tella and Obaleye, 2010) not as a result of coordination. This indicates that NH<sub>2</sub> is probably not involved in coordination. The ν(C=N) band of the quinoline N(1) at 1595 cm<sup>-1</sup> in the Trimethoprim shifted to a higher wavenumber upon complexation in all complexes synthesized by both

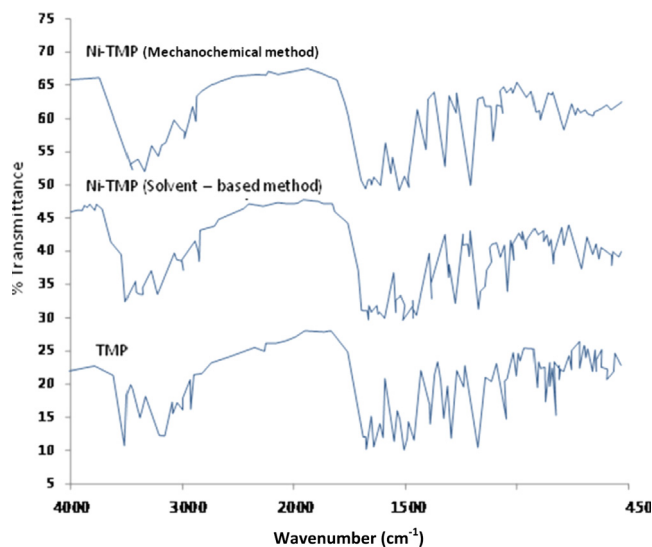


**Figure 3** FTIR spectra of Cu-TMP (Mechanochemical method), Cu-TMP (Solvent-based) and TMP.

methods. The presence of acetate in the coordination sphere of all the complexes is confirmed by ν<sub>asym</sub>(COO) band between 1630–1668 cm<sup>-1</sup> compared to 1578 cm<sup>-1</sup> for CH<sub>3</sub>COONa and ν<sub>sym</sub>(COO) at 1462–1472 cm<sup>-1</sup> compared to 1414 cm<sup>-1</sup> for CH<sub>3</sub>COONa. Difference in ν<sub>asym</sub>–ν<sub>sym</sub> which is around 168–196 cm<sup>-1</sup>, shows that Δν values in this case were found to be less than 200 indicating bidentate bridging coordination of acetate group. The metal-nitrogen and metal-oxygen bands are indicated by the appearance of new bands of ν(M–N) and ν(M–O) stretching vibration observed around 665–681 cm<sup>-1</sup> and 529–534 cm<sup>-1</sup> respectively, in the spectra of mechanochemical and solution based complexes. This is probably due to the coordination of metal ion through Nitrogen of the pyrimidine (N<sup>1</sup>) and oxygen of the acetate ion. This mode of coordination has also been found in metal complexes of Trimethoprim synthesized previously in solvent medium (Naldini et al., 1984). It can be inferred that IR spectra for mechanochemically-prepared complex were essentially identical to that of conventional solution based material except that there are two additional peaks between 3500 and 3600 cm<sup>-1</sup>, this may probably be due to methanol molecules present in the products of solvent-based synthesis. This is in agreement with elemental analysis results.

#### 4.2. Electronic spectra and magnetic susceptibility

The electronic spectra in DMSO of the ligand and the complexes using mechanochemical and solution method are shown

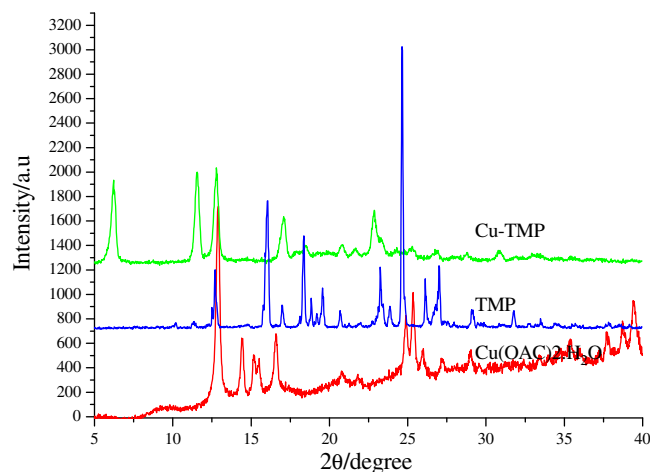


**Figure 4** FTIR spectra of Ni-TMP (Mechanochemical method), Ni-TMP (Solvent-based) and TMP.

in Table 2. The ligand gave one absorption band ( $36364\text{ cm}^{-1}$ ) at 275 nm due to  $\pi-\pi^*/n-\pi^*$  (overlap of the two peaks) transitions within the benzene ring and C=N of the pyrimidine group (Tella and Obaleye, 2010). In all the complexes Trimethoprim exhibits similar band at the same region but appears on the shorter wavelength side (hyperchromic shift) due to complexation. The visible region spectra of the complexes 1 and 1.CH<sub>3</sub>OH produced one additional band in the region (760–780 nm) which is attributed to  ${}^2E_g \rightarrow {}^2T_{2g}$  suggesting an octahedral structure around the metal ion. The electronic configuration of complexes 2 and 2.CH<sub>3</sub>OH is  $d^8$  and spectroscopic ground term is  ${}^3F$ . There are three electronic transitions between 400–800 nm in the visible region. The assignments are in conformity with the proposed octahedral geometry for two nickel complexes. The magnetic moment found for the two complexes of Cu(II) is in the range of 2.30–2.40 $\beta$  and that of Ni(II) is in the range of 4.78–4.80 $\beta$  these values suggest an octahedral geometry which is in good agreement with data of electronic transition (Lever, 1984).

#### 4.3. X-ray powder diffraction studies

The occurrence of a reaction was ascertained by comparison of the XRPD patterns of the product to those of the reactants. XRPD patterns of  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$  were compared



**Figure 5** Comparison of XRPD patterns for: (a) Cu-TMP ( $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$ ) prepared by mechanochemical solvent-free synthesis, (b) TMP, (c)  $\text{Cu}(\text{OAC})_2 \cdot \text{H}_2\text{O}$ .

with that of Trimethoprim and copper acetate monohydrate as shown in Fig. 5.

No peaks due to starting materials were observed, suggesting that a reaction had occurred.

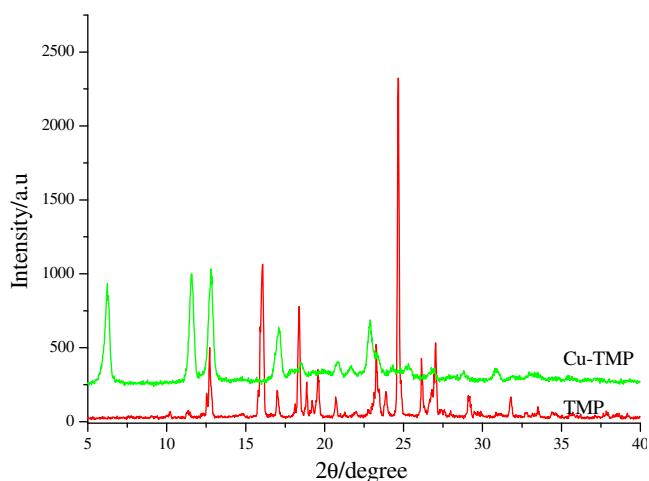
The X-ray powder diffraction pattern of  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$  was different from that of the ligand Trimethoprim. New peaks corresponding to complex are observed. XRPD pattern in Fig. 6 shows peaks at  $2\theta = 6, 11, \text{ and } 26^\circ$  indicating formation of a new phase. This suggests that complexation of Trimethoprim with copper acetate most probably occurred. The single crystal diffraction data for  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$  were obtained from the Cambridge crystallographic database (CCD). The CCD letter code for this structure is HAGRUD. Its XRPD pattern was simulated from the single crystal data using Mercury 1.3 software. The HAGRUD single crystal structure was previously reported by Naldini et al., 1984.

The simulated patterns for  $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$  were essentially identical to that of the mechanochemically-prepared material (Fig. 7) except that there are two additional peaks at  $2\theta = 12.5^\circ$  and  $18.5^\circ$  in the simulated which appear to be due to methanol molecules. This is consistent with the results obtained from elemental analysis and infra red spectroscopy.

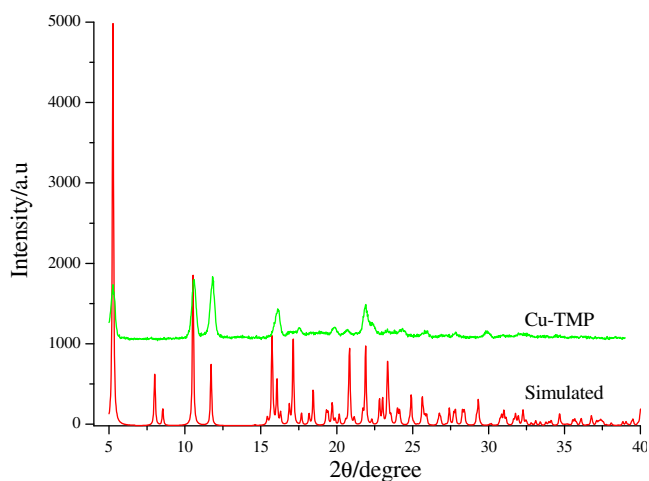
It is notable therefore that in this case the mechanochemical synthesis appeared to give a purer product.

**Table 2** UV–Visible spectra of Trimethoprim and its metal complexes.

S/N	Complex/Ligand	Method	Wavelength ( $\text{nm}^{-1}$ )	Energy ( $\text{cm}^{-1}$ )	Assignment
1	TMP		275	36364	$\pi-\pi^*/n-\pi^*$
2	1.	Mechanochemical	268	37313	$\pi-\pi^*/n-\pi^*$
			767	13038	${}^2E_g \rightarrow {}^2T_{2g}$
3	1.CH <sub>3</sub> OH	Solvent-based	272	36765	$\pi-\pi^*/n-\pi^*$
			774	12919	${}^2E_g \rightarrow {}^2T_{2g}$
4	2.	Mechanochemical	432	23148	${}^3A_{2g} \rightarrow {}^3T_{1g}(\text{P})$
			556	17986	${}^3A_{2g} \rightarrow {}^3T_{1g}(\text{F})$
			785	12739	${}^3A_{2g} \rightarrow {}^3T_{2g}(\text{F})$
5	2.CH <sub>3</sub> OH	Solvent-based	410	24390	${}^3A_{2g} \rightarrow {}^3T_{1g}(\text{P})$
			570	17544	${}^3A_{2g} \rightarrow {}^3T_{1g}(\text{F})$
			700	14286	${}^3A_{2g} \rightarrow {}^3T_{2g}(\text{F})$



**Figure 6** Comparison of XRPD patterns: (a) Cu-TMP ( $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$ ) prepared by mechanochemical solvent-free synthesis (b) TMP (Trimethoprim).



**Figure 7** Comparison of XRPD patterns: (a) Cu-TMP ( $[\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2]$ ) prepared by mechanochemical solvent-free synthesis, (b) Simulated pattern from the single crystal X-ray structure of  $\text{Cu-TMP}([\text{Cu}(\text{OOCCH}_3)_2(\text{TMP})_2] \cdot \text{CH}_3\text{OH}$ .

## 5. Conclusions

We have demonstrated the utility of mechanochemical synthesis approach for coordination complexes of active pharmaceutical ingredients (API). It was discovered that a solvent free solid–solid state can be used to obtain the same product as that obtained for the solvent based method. As evidenced from melting point and elemental analysis data, the results obtained by mechanochemical synthesis were identical to those obtained from solution based synthesis. For all complexes, the obtained infra red data showed that coordination involved two molecules of Trimethoprim through the nitrogen atom of pyrimidine group as well as acetate ions from the metal salts to give an octahedral structure. In both cases the resulting products obtained via ball-milling exhibited the same XRPD patterns as products obtained via solution synthesis. In contrast to complexes from solution, however, the products obtained by ball-milling did not require any purification procedure

(i.e. filtering). Therefore, it can be concluded that the structure of the mechanochemically synthesized sample is comparable to those obtained in solution.

In summary, the mechanochemical approach proved to be a reliable and effective strategy for the synthesis of metal–drug complexes. As well as being a quick and easy procedure, it offers quantitative yields and products of high quality.

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