Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (3): 1289-1294

(International Peer Reviewed Journal)

The New Synthetic Utility of PCM Drug for Metal Complexation

Pravinsing S. Girase and Deepak V. Nagarale*

P.G. Research Centre, Z. B. Patil College, Dhule K.B.C. North Maharashtra University, Jalgaon, Maharastra, **INDIA**

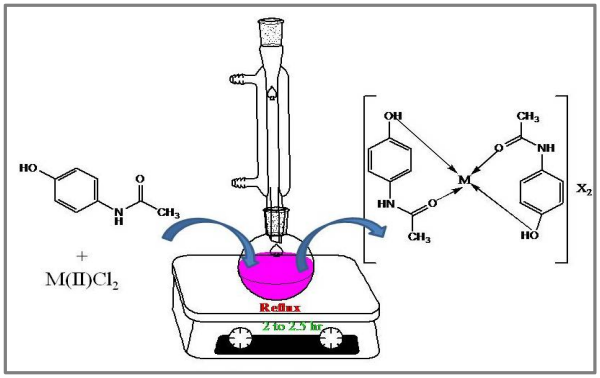
Email:nagaraledeepak01@gmail.com

Accepted on 5th May, 2019

ABSTRACT

Paracetamol (PCM) also known as Acetaminophen and N-(4-hydroxyphenyl) acetamide is a derivative of 4-aminophenol and is one of the most frequently commercialized antipyretic and analgesic drug. Here, we have synthesized the PCM drug and elaborate its various synthetic utility towards the formation metal complexes by new modified method by using ethanolic HCl gave reaction rate faster than pervious known methods. The synthesized compounds were characterized by spectral analysis.

Graphical Abstract



Keywords: Paracetamol(PCM), Medicinal Chemistry, Metal Complexes, Bidentate Ligand.

INTRODUCTION

Paracetamol (Acetaminophen) is a gentle analgesic with weak anti-inflammatory activity, usually used for the release of aches and pains. Paracetamol (PCM) is broadly used as antipyretic and analgesic drug in the medicinal practices shown in figure 1[**1**]. But excess doses of PCM may result in some side effects such as accumulation of toxic metabolites, causing severe, fetal hepatoxicity and nephrotoxicity olaleye [**2**]. Thus, resolve of PCM is of so much importance for quality control and medical control. A variety of analytical methods have been developed for capable and responsive determination of PCM such as spectrophotometry [**3**], chemiluminescence [**4**], flow-injection analysis [**5**] and chromatography [**6**]. However, the above methods are either time-consuming or require

pretreatment. Hence, it is of great significance to develop sensitive, efficient, facile and accurate analytical methods for the detection of PCM.

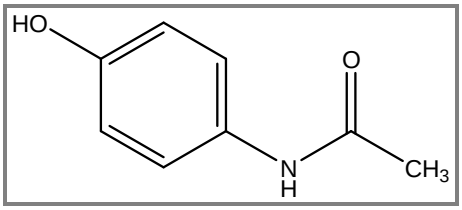


Figure 1. N-(4-hydroxyphenyl) acetamide(PCM)

Acetaminophen (Paracetamol, N-(4-hydroxyphenyl) acetamide) is a derivative of 4-aminophenol and is one of the most frequently commercialized antipyretic and analgesic agent without medical prescription. Acetaminophen is used as an active ingredient in different pharmaceutical formulations with different routes of administration, such as tablets and capsules, suspension, intravenous and intramuscular form, as well as rectal suppositories [**7**]. Acetaminophen (PCM) is commonly used as a main ingredient in cold and influenza pharmaceutical formulations [**8**] and is recommended in treatment of headache, toothache, rheumatism and neuralgia [**9**]. In combination with other active substances, acetaminophen can also be used in the amelioration of post-operative pain [**10**] or providing palliative care for patients that suffers for advanced forms of neoplasms [**11**]. Even if PCM is not considered an NSAID due to the fact that its anti-inflammatory activity is considered weak comparative to other drugs in this class, studies had shown that PCM is a selective cyclooxygenase-2 inhibitor [**12**]. The chemical structure of PCM is presented in figure 1. The interaction between metal ions and pharmaceuticals is an attractive field of research, due to the fact that in vivo, metal ions can interact with pharmaceutical ligands that appear in living systems. It is known that the cations can bind to enzymes, proteins and other biological ligands [**13**].

The chemistry of coordination compounds is a domain that has known a rapid development in the last decade. Metal coordination compounds that contain active substances as ligands are the base of inorganic medicinal chemistry, Heterocyclic pyridine, Pyrrole and represent a highly developing domain with enormous potential for applications in medicine, engineering or agriculture [**14-17**] and Heterocyclic synthesis [**18-20**].

MATERIALS AND METHODS

Experimental: All chemicals were of analytical grade. Acetaminophen and anhydrous zinc chloride were obtained from Sigma- Aldrich and used as received and synthesized also. The M (II) content was determined by complexometric titration with EDTA, in buffer solution (NH_3/NH_4Cl) at pH ~ 10, in the presence of Eriochrome Black T as indicator, by a standard analytical procedure.

General procedure

Synthesis of the metal complex: The complex was obtained in the reaction of PCM and metal chloride in aqueous medium. To a solution (100 mL) containing anhydrous metal chloride (0.409 g, 3 mmol) in water, solid PCM (0.907 g, 6 mmol) was added. The mixture was stirred at room temperature until the dissolution of PCM occurred, then heated under reflux for 2-2.5h. The mixture was allowed to cool down at room temp. This was filtered, washed with methanol and dried over silica gel. The same procedure was used for the preparation of Co(II), Ni(II), Cu(II), and Zn(II) complexes from their chloride, acetate and nitrate salts respectively

At the beginning there is development of a new solvent and reagent used in system. During the preliminary studies optimization was done with different reagent system shown in table 1 and table 2 shows yield and reaction condition for substrate study. The important part towards determination of

reaction conditions such as the catalyst, catalyst loading, solvent, temperature and time (Table 1). Initially reaction subjected to 2:1 molar quantities. Thus complex formation is excellent with Ethanolic HCl giving maximum yield of product with 120 min reaction time (Table 4, entry 9) but after increasing reaction time up to 140 yield not increased. We further made study on substrate (Table 2 entry 3, 4 and 5) it shows the behavior of different metal with PCM drug with time spend for reaction shown in table 2.

Table 1. Optimization of reaction parameters[a]

Entry	Solvent	Time(min)	Yield(%)[b]
1	--	20	--
2	Ethanol	05	
3	Methanol	10	60
4	Ethanolic \HCl	50	56
5	Ethanol	25	60
6	Ethanol.HCl	60	72
7	Methanol	30	58
8	H_2O	15	--
9	Ethanolic.HCl	**120**	**94**
10	Ethanolic.HCl	140	994

Reaction Condition [a]: PCM (0.02 mol), Metal Cholride (0.01 mmol), Ethanolic.HCl (10mL), Isolated Yield[b].

Table 2. Substrate study of metal complex[a]

S. No.	Metal Chloride M(II)	Time (Min)	Colour	Yield (%)[b]	M.P. (^{0}C)
1	Cu	120	Greenish	94	185°C
2	Zn	140	Off White	90	110°C
3	Co	120	Brown	89	140°C
4	Ni	120	Greenish	94	155°C
5	Mn	120	White	96	110°C

Reaction Condition [a]: Metal Chloride (0.01 mol), PCM(0.01mol), Ethanolic.HCl(10mL), Isolated Yield[b].

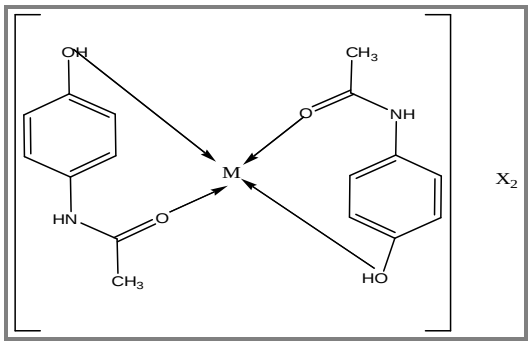
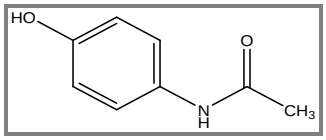
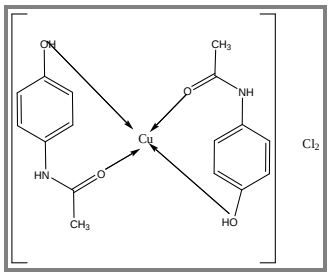
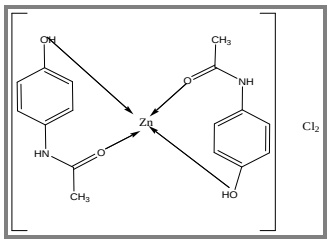
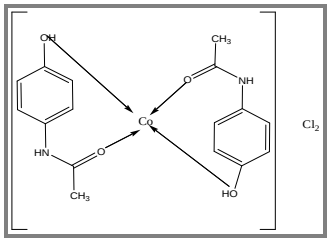
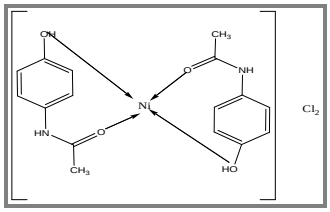
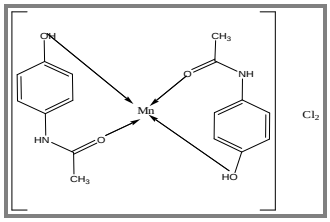


Figure 2. Proposed general structure of metal complex**.**

RESULTS AND DISCUSSION

By the analysis of the FTIR spectrum of Cu(II) proposed metal complex (Figure 2), the maximum of several bands have been shifted to different cm^{-1}. The disappearance or superpose of the characteristic bands of –OH stretching vibrations from 3337 cm^{-1} and the appearance of o broad signal between 3321 cm^{-1} indicates both the involvement of the –OH group in the formation of the coordination complex and suggest the presence of water in its structure. A significant shifting to a higher wave

Characterization of synthesized compounds:

Entry	Structure	Nature	Melting Point	I.R.	Colour
1		Crystalline	169 ^{O}C.	3337, 1429, 5400-3200, 1258, 3000-2850, 1627.	White
2		Crystalline	185 ^{O}C.	3600-3200,1435, 3400-3200, 3000-2800, 1258, 1652.	Greenish
3		Crystalline	110 ^{O}C.	3600-3200, 1436, 3400-3200, 1257, 3000-2800, 1651.	Off White
4		Crystalline	140 ^{O}C.	3600-3200, 1434, 3400-3200, 3000-2800, 1258, 1652.	Brown
5		Crystalline	155 ^{O}C.	3600-3200, 1435, 3400-3200, 1225, 3000-2800, 1651.	Greenish
6		Crystalline	110 ^{O}C.	3321, 1453, 3157,1258, 3000-2800, 1651	White

number suggest the presence of water in its structure. A significant shifting to a higher wave number (1627 cm^{-1}) of the characteristic stretching band of C=O functional group suggest that coordination occurs through this group. A comparative analysis of the corresponding wave numbers of other bands from PCM and metal complex reveals only insignificants shifting (at ± 3 cm^{-1}) and cannot be assigned

to involvement in coordination bonds. In order to sustain the formation of the metal complex, two new absorption bands at 650 cm^{-1}. IR shown in figure 3.

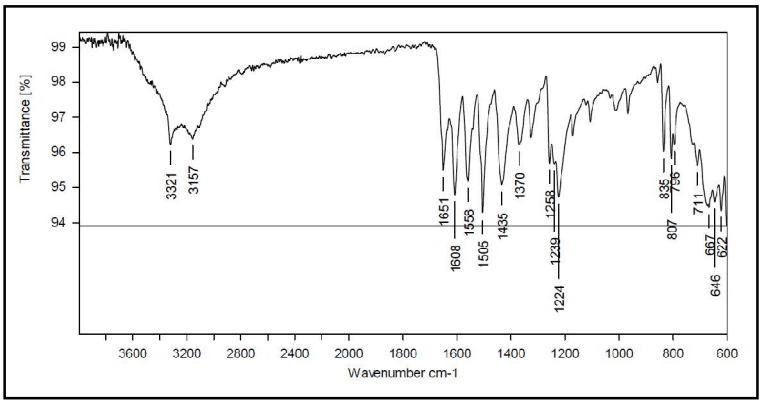


Figure 3. Infrared (IR) spectrum.

Metal Complex 1: $[Cu(PCM)_2]Cl_2$, Color: Greenish (94%), M.P.: 185^{O}C, **IR:** 3600-3200, 1435, 3400-3200, 3000-2800, 1258, 1652, **^{1}H NMR**: 2.28(s,3H),8.13(s,1NH),7.81(d,2H),6.84(d,2H), **^{13}C NMR:** 17(CH_3), 147(CO), 135(1C),130(2C), 124(2C),146(1C).

APPLICATION

In this paper, we have synthesized the PCM drug and elaborate its applications to various synthetic utility towards the formation metal complexes. We have also modified existing method with new method which is reduced reaction time using ethanolic HCl.

CONCLUSION

Heteroleptic metal(II) complexes of Paracetamol (PCM) analyzed as $[M(L)(PCM)X_2]$, where X = Cl M = Mn, Co, Ni, Cu and Zn based on percentage metal and conductance measurements. Infrared and electronic spectroscopy. The synthesis was made with ethanolic HCl give reaction rate faster than pervious known methods.

ACKNOWLEDGEMENTS

The authors are greatly thankful to Principal and Head, Department of Chemistry JET's Z.B. Patil College, Dhule for providing the laboratory facilities for this work

REFERENCES

[1]. L.Özcan, Y. Sahin, Determination of Paracetamol Based on Electropolymerized-Molecularly Imprinted Polypyrrole Modified Pencil Graphite Electrode. Sens, *Actuators B.*, **2007**, 127, 362-369.

[2]. M. T. Rocha, B. T. J. Acetaminophen-Induced Liver Damage in Mice: Effects of Some Medicinal Plants on the Oxidative Defense System, *Exp. Toxicol. Pathol.*, **2008**, 59, 319–327.

[3]. A. R. Sirajuddin, K. haskheli, A. Shah, M. I. Bhanger, A. Niaz, S. Mahesar, Simpler Spectrophotometric Assay of Paracetamol in Tablets and Urine Samples, *Spectrochim, Acta A* **2007**, 68, 747–751.

[4]. A. Goyal, S. Jain, Simultaneous Estimation of Paracetamol, Chlorzoxazone and Diclofenac Sodium in Pharmaceutical Formulation by a Novel HPLC Method, *Acta Pharm. Sciencia*., **2007**, 49, 147–151.
[5]. M. Knochen, J. Giglio, B. F. Reis, Flow-Injection Spectrophotometric Determination of Paracetamol in Tablets and Oral Solutions, *J. Pharm. Biomed. Anal.*, **2003**, 33, 191–197.
[6]. D. Easwaramoorthy, Y. C. Yu, H. Huang, J. Chemiluminescence Detection of Paracetamol by a Luminol-Permanganate Based Reaction, *Anal. Chim. Acta.*, **2001**, 439, 95–100.
[7]. a)Acetaminophen. Physicians' Desk Reference, 63rd Ed. Montvale, NJ: Thomson PDR, 2009, P. 1915. b) P. Moller, , S. Sindet Pedersen, C. Petersen, ,G. Juhl, A. Dillenschneider, L. Skoglund, Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery Brit. J. Anaesth., **2005**, 94 (5), 642.
[8]. H. Mizoguchi, A. Wilson, G. R. Jerdack, J. D. Hull, M. Goodale, J. M. Grender, B. A. Tyler, Efficacy of a single evening dose of syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulfate in subjects with multiple common cold symptoms, *Int. J. Clin. Pharmacol. Ther.*, **2007**, 45(4), 230.
[9]. a) K. Harminder, D. Kanav, K. Jaspreet, M. Bharti, C. Ashish, Synthesis and solid-state characterization of platinum complexes with hexadentate amino- and iminophosphine ligands, *Am. J. Drug Discovery Dev.*, **2013**, 3, 13. b) A. Lawal, J. A., Obaleye, Synthesis and solid-state characterization of platinum complexes with hexadentate amino- and iminophosphine ligands, *Biokem*, **2007**, 19, 9.
[10]. D. Hynes, M. Mccarroll, O., Hiesse-Provost, Analgesic efficacy of parenteral paracetamol (propacetamol) and diclofenac in post-operative orthopaedic pain, Acta Anaesthesiol, *Scand.* **2006,** 50(3), 374.
[11]. B. Axelsson, , P. Stellborn, G. Ström, Analgesic effect of paracetamol on cancer related pain in concurrent strong opioid therapy. A prospective clinical study, *Acta Oncol.*, 2008, 47(5), 891.
[12]. B. Hinz, O. Cheremina K. Brune, Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man, *Faseb J.* **2008**, 22(2), 383.
[13]. G. M. Stephenson, B. A. Diseroad, Diseroad, Structural relationship and desolvation behavior of cromolyn, cefazolin and fenoprofen sodium hydrates, *Int. J. Pharm.*, **2000**,198, 167.
[14]. Frausto Da Silva, J. J. R. Williams, R. J. P., The Biological Chemistry Of The Elements: The Inorganic Chemistry of Life, Oxford University Press, **2001**.
[15]. A. P. Rajput, D. V. Nagarale, Synthesis, Characterization and Antimicrobial study of piperidine-2,6-diones derivatives, *Der Pharma Chemica*, **2016**, 8(8), 182-186.
[16]. A. P. Rajput, D. V. Nagarale, Thermal Condensation of Enaminoimine Hydrochlorides of 2,6-Dichloro-3,5-diformyl (N-Substituted Phenyl)pyridines, *Chem Sci Trans.*, **2016**, 5(4), 912-917.
[17]. A. P. Rajput, D. V. Nagarale, Synthesis Of 2,2'-{[2,6-Dichloro-1-(Substitutedphenyl)-1,4-Dihydropyridine-3,5-Diyl] Dimethylylidene} Dipropanedinitrile Using Green Catalyst L-Proline-Fe_3O_4 MNP, *J. Applicable Chem.*, **2018**, 7 (6), 1592-1596.
[18]. A. P.Rajput, D. V.,Nagarale, Synthesis, Characterization and Antimicrobial study of piperidine-2,6-diones derivatives, *Der Pharma Chemica*, **2016**, 8(8). 182-186.
[19]. A. P. Rajput, D. V. Nagarale, A Novel Synthesis of N-substituted Glutarimides using $ZnCl_2$ Catalyst: A green approach, *IJPC*, **2016**, 06 (07), 181-185.
[20]. A. P. Rajput, D. V. Nagarale., Thermal Condensation of Enaminoimine Hydrochlorides of 2, 6-Dichloro-3, 5-diformyl (N-Substituted Phenyl) pyridines, *Chem Sci Trans*., **2016**, 5(4), 912-917.