

## Fe (III) complex of nateglinide: Synthesis and characterization

Shruti S Sarwade \*, W. N Jadhav and B.C. Khade

*Department Of Chemistry, Dnyanopasak Science College, Parbhani, Maharashtra, India*

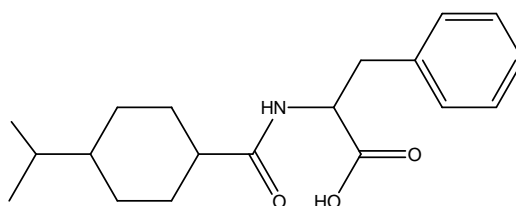
### ABSTRACT

*The Fe (III) complex of ligand Nateglinide has been synthesized and characterized by physiochemical properties, elemental analysis, IR, UV and thermogravimetric analysis. The data suggests that the complex is octahedral in geometry.*

**Keywords:** Nateglinide, complex, spectral study.

### INTRODUCTION

Nateglinide is a drug for the treatment of type 2 diabetes. Nateglinide was developed by Ajinomoto, a Japanese company and is old by the Swiss pharmaceutical company Novartis. Diabetes mellitus type 2 formerly non- insulin dependent diabetes mellitus (NIDDM) or adult – onset diabetes is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and relative lack of insulin. This is contrast to diabetes mellitus type 1, in which there is an absolute lack of insulin due to breakdown of islet cells in the pancreas. Nateglinide belong to the meglitinide class of blood glucose-lowering drugs.



3-phenyl-2-[(4-propan-2-ylcyclohexanecarbonyl)amino]propanoic acid

**Figure 1. Structure of Nateglinide**

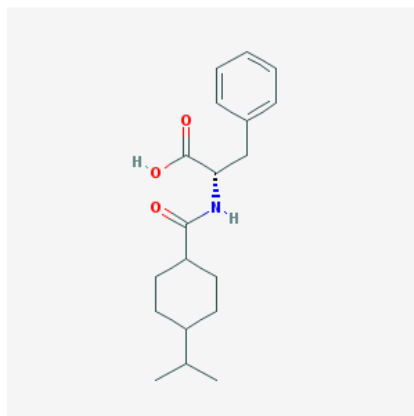


Figure 2. 2D structure of Nateglinide.

Nateglinide is short acting, pancreatic, beta cell selective, KATP potassium channel blocker that improves overall glycemic control in type 2 Diabetes. Although Nateglinide mechanism of action is related to that of sulfonylureas, important differences do exist. Nateglinide binds rapidly to the sulfonylureas SUR, receptor with a relatively low affinity, and it dissociates from it extremely rapidly in a matter of seconds. Nateglinide has a rapid onset and short duration of action on beta cells in stimulating insulin secretion in vivo and providing good control, while the short duration avoids delayed hyperinsulinemia and hypoglycemia after meals. Nateglinide is not a sulfonylurea, but it shares the mechanism of action of commonly used oral hypoglycemic agents such as glibenclamide and glipizide. Like the recently introduced, short acting agent repaglinide, it does not incorporate a sulfonylurea moiety. Compounds with such a profile should not only achieve improved overall glucose control, but also reduce the risk of vascular complications which is most important feature of Nateglinide. Nateglinide is both effective and well tolerated in the treatment of type 2 diabetes. Clinical comparisons of these agents have shown Nateglinide to be more effective in attenuating postprandial glucose than any other oral hypoglycemic agent, and that treatment with Nateglinide provides effects that afford improved control of plasma glucose levels. [1-4]

## MATERIALS AND METHODS

### Materials:

All chemicals used in this study were of analytical grade. They included Nateglinide (NAT) of the formula  $C_{19}H_{27}NO_3$ , 317.42g/mol and metal salt  $FeCl_3 \cdot 6H_2O$ . These chemicals were purchased from Merck or Aldrich. The organic solvent ethanol was purchased from BDH and used without further purification.

### Method:s

The solid complex was prepared by drop wise addition of 25ml of 1mM metal salt to 25ml of 2mM of Nateglinide solution.

2mM solution in 25 ml ethanol was made by dissolving 0.63gm and metal salts solution by dissolving 0.278 gm.  $FeCl_3 \cdot 6H_2O$  in 25ml ethanol while preparing complex. The complex was synthesized by refluxing Nateglinide and metal salt. Nateglinide is dissolved in ethanol and to this metal solution in ethanol was added in the ratio 1:2 [M: L], with continuous stirring, refluxed on water bath at  $150^{\circ}C$ . The resulted solution was cooled, filtered and later reduced to a small volume. The concentrated solution was left overnight, which resulted in the formation of complex.

## RESULTS AND DISSCUSSION

Table 1: Some physical properties of Nateglinide and its metal

Compound	M.P $^{\circ}C$	Colour	Magnetic moment B.M	conductivity $\Omega^{-1}cm^2mol^{-1}$
Nateglinide (Nat)	380 $^{\circ}C$	White	-	-
$[Fe (Nat)_2 (H_2O)_2]$	455 $^{\circ}C$	Brown	5.3	$1.597 \times 10^{-4}$

Table 2: Elemental analysis of complex

Compound	%C cal(found)	%H cal(found)	N% cal(found)	O% cal(found)	M% cal(found)
Nateglinide (Nat)	71.92(72)	8.51(8.65)	4.41(4.50)	15.14(15.23)	-
[Fe (Nat) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	62.80(63)	7.43(7.75)	3.85(3.92)	13.22(13.30)	7.71(7.86)

**UV/VISIBLE SPECTRAL STUDIES:**

Iron, Fe (III) is a moderately oxidizing ion and many of its complexes exhibit ligand to metal charge transitions (L→MCT). In most cases, the d-d absorption in octahedral Fe (III) complexes is rarely observed because the (L→MCT) obscure it. Furthermore, High Spin Fe (III) complexes are not stabilized by crystal field effects. Charge transfer transition in Fe (III) complexes occur between 45000 – 26000 cm<sup>-1</sup>. The electronic spectrum of [Fe (Nat)<sub>2</sub> (H<sub>2</sub>O)<sub>2</sub>] showed absorption in the region 30,000 – 34000 cm<sup>-1</sup> that is attributed to L→MCT.

High spin Fe (III) complexes in general have magnetic moments at room temperature close to 5.9 B.M and somewhat in excess of 2 B.M due to orbital contribution if they are low spin. A magnetic moment of 5.2 B.M for [Fe (Nat)<sub>2</sub> (H<sub>2</sub>O)<sub>2</sub>] indicates a high spin octahedral complex.

Table 3: UV/ Visible spectral assignment of Nateglinide and its complex

Compound	Wavelength (nm)	cm <sup>-1</sup>
Nateglinide (Nat)	264	37878
	254	39370
	210	47619
[Fe (Nat) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	296	33783
	322	31055
	346	28985

**IR SPECTRA ANALYSIS**

The careful inspection of the IR spectra of free Nateglinide and its complex is based on some general references and made in comparison with other related molecules and complexes.

FTIR of Nateglinide shows the principal peaks at wave numbers of 1213-1386 cm<sup>-1</sup> justifying the presence of carboxyl, amino and carbonyl. C-H stretching is between at 2857-3030 cm<sup>-1</sup>. Amide C=O vibration at 1723 cm<sup>-1</sup> and N-H stretching appeared at 3296 cm<sup>-1</sup>. Prominent peaks at 1643cm<sup>-1</sup>, 1296cm<sup>-1</sup> and 1446cm<sup>-1</sup> were appeared due to C=O, C-O and C-O-H stretching in acidic group.

In Nateglinide Iron complex the amide carbonyl at 1723 cm<sup>-1</sup> is not shifted supporting the non-involvement of the amide carbonyl in the metal coordination. The  $\nu_{as}$  (COO<sup>-</sup>) 1575cm<sup>-1</sup> and  $\nu_s$  1390cm<sup>-1</sup> (COO<sup>-</sup>) difference  $\Delta\nu < 200$  indicated bidentate behavior. This band appears broadened in the most of the chelates by the simultaneous appearance of the  $\delta$  (H<sub>2</sub>O)vibration in the same range, a fact which obstructs the clear visualization of the effective displacement of the  $\nu$  (C=O) band. New vibrating absorption at 609cm<sup>-1</sup> indicates presence of M-O bond in the complex.

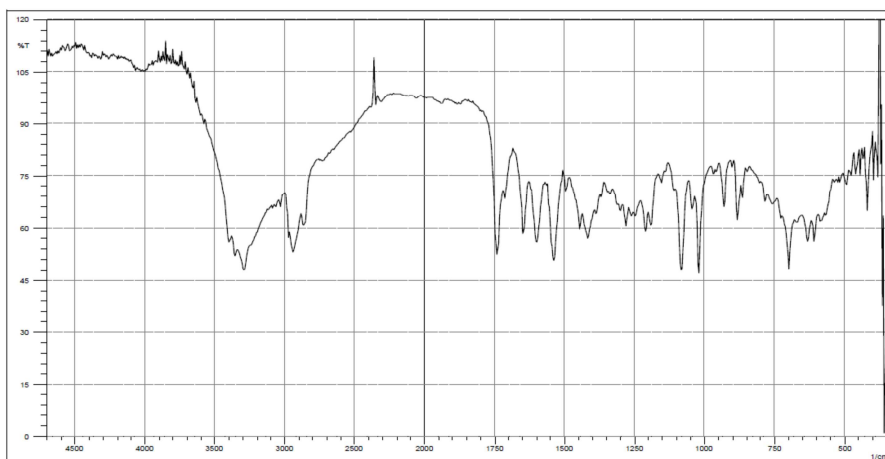
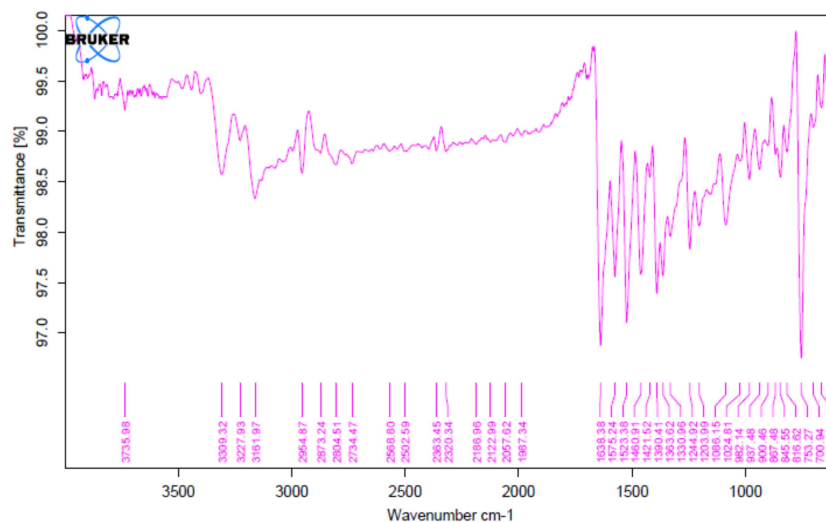


FIGURE 5: FTIR SPECTRA OF NATEGLINIDE

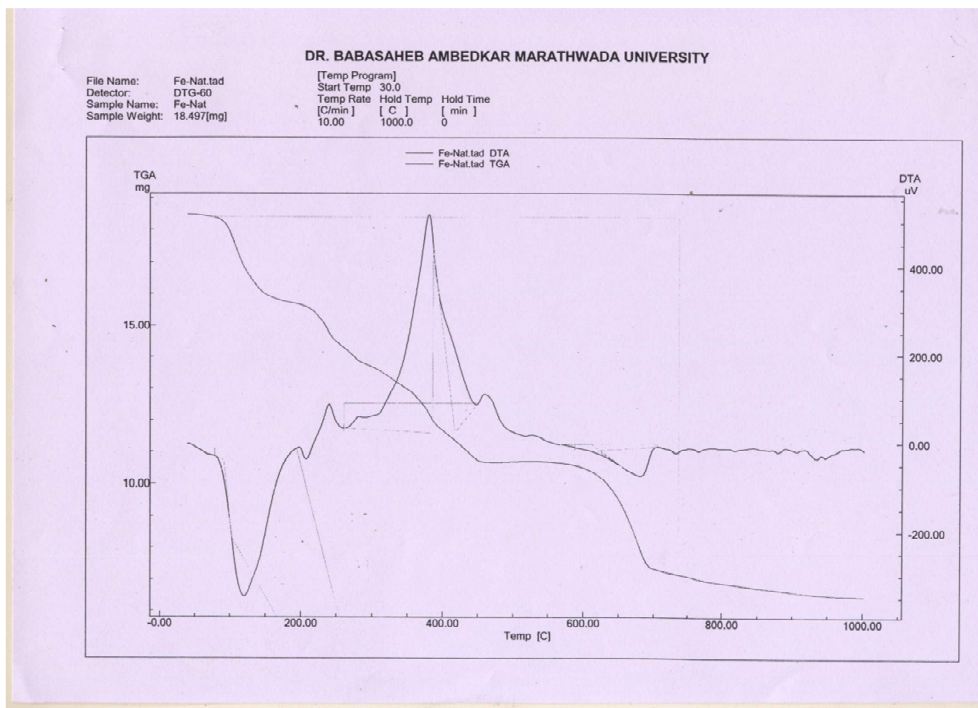
Graph1. IR Spectra of Nateglidine



Graph 2: IR Spectra of complex.

**THERMOGRAVIMETRIC STUDIES:**

The mode of coordination of ligand in the complex is supported by Thermogravimetric studies. The complex has observed loss in weight in 140-200 °C temperature range, coincides with the removal of two molecules of water. TG curve of this complex reveal that they remain unchanged up to 200°C. This complex show gradual decomposition till 200°C, but above this temperature the rate of decomposition is found increased and practically at 450°C the weight loss is 34.33% has been observed which is consistent with the removal of propan -2- yl cyclohexane molecule from the above complex. Further, a slow decomposition has continued and mass loss takes place at 680°C which is evident from the TG curve of the complex. The DTA graph shows endotherms and exotherms and endotherms depict decomposition of ligand and anions.<sup>5-8</sup>



Graph 3: TG/DTA Spectra of the complex.

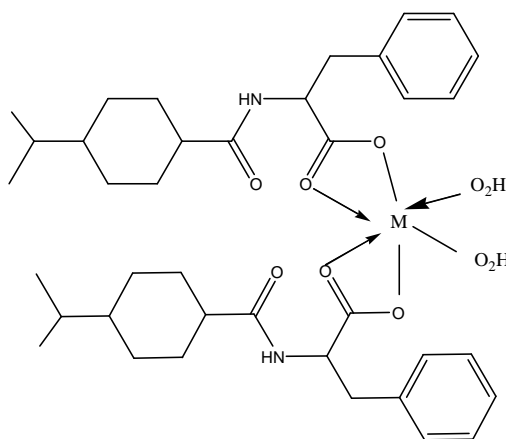


Figure 3: Proposed Structure of complex

**CONCLUSION**

The drug Nateglinide formed complex with Fe(III) of general formula  $[Fe (Nat)_2 (H_2O)_2]$ . The complex was synthesized and characterized by elemental analysis, molar conductivity, magnetic susceptibility measurements, UV

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and IR spectra analysis. The complex has octahedral geometry. The thermogravimetric analysis supports the structure and also confirms of two coordinated water molecules.

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