Synthesis, characterization and antiinflammatory effects of Cr(III), Mn(II), Fe(III) and Zn(II) complexes with diclofenac sodium

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Complexes of diclofenac sodium, \([2-\{2,6\text{-dichlorophenyl}\text{-amino}1\text{ benzeneacetic acid monosodium salt}\},\) an antiinflammatory drug, with Cr(III), Mn(II), Fe(III) and Zn(II) have been prepared and characterized by elemental analysis, magnetic susceptibility, molar conductance, electronic and infrared spectroscopy. The drug functions as bidentate anionic ligand. Antiinflammatory effects have been evaluated by carrageenan-induced rat paw oedema test. The complexes of Cr(III) and Zn(II) have been found to be more effective than the drug itself.

It has been reported that complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug\(^{1,2}\). Diclofenac sodium is a non-steroidal antiinflammatory drug (NSAID), widely used as antiinflammatory and analgesic agent\(^3\). Several complexes of this drug have been found more active\(^5\) (Structure I).

In view of the increasing importance of drug complexes, a detailed study of the interaction of Cr(III), Mn(II), Fe(III) and Zn(II) with diclofenac sodium was undertaken. Antiinflammatory activity of the complexes has been carried out to see the change in activity due to complexation (Structure II,III).

Experimental

All the chemicals used were of AR grade. The ligand Diclofenac sodium was obtained from Aristo Pharmaceutical, Mumbai and used as such.

Preparation of complex

The stoichiometric ratio of the complexes were determined by spectrophotometric/conductometric methods. Cr(III), Mn(II), Fe(III) and Zn(II) complexes were prepared by refluxing aqueous solution of metal salt and the ligand in the molar ratio 1:2 for Cr(III), Fe(III) and Zn(II) and 1:1 for Mn(II) complexes-2h on a water bath. The pH was maintained \(\sim 5-8\) by adding dil NH\(_2\)/HCl. The precipitated complexes were washed with water and finally with ether and dried under reduced pressure at room temperature. The purity of the compounds was monitored by TLC using silica gel.

Melting points were determined on a Tosniwal CL-0301 apparatus. Molecular weights of the complexes were determined by Rast’s camphor method\(^9\). Elemental analysis were carried out on a Heraeus Carlo Erba 1108 analyser at RSIC, CDRI Lucknow.

Metal and chloride contents were determined by standard methods\(^10\). The IR spectra were recorded on Shimadzu 8201 PC infrared spectrophotometer in KBr between the range 400-4000 cm\(^{-1}\). Electronic spectra were recorded on Shimadzu 210 A UV/VIS Spectrophotometer. Molar conductance (in \(10^3\) M DMF) was determined using an Elico CM 82 T instrument. Magnetic susceptibility was measured on Gouy’s balance at room temperature using CuSO\(_4\).
The molar conductance in DMF of Cr(III) is 92.88 ohm·cm² mol⁻¹ which indicates its 1:1 electrolytic nature. Mn(II), Fe(III) and Zn(II) complexes are non-electrolytic in nature. The presence of chloride ion in Cr(III) complex has been confirmed by elemental analysis.

As expected, the Zn(II) complex is diamagnetic while other complexes are paramagnetic. The room temperature magnetic moment value (3.87 B.M.) of Cr(III) complex is close to the spin only value for octahedral complex. Those of the Mn(II) (5.86 B.M.) and Fe(III) (5.81B.M.) complexes are in the range required for six-coordinated spin-free octahedral complexes.

In the electronic spectra, Cr(III) complex exhibits three bands at 13800, 18100 and 19200 cm⁻¹ corresponding to the transitions $^4A_{2g}(F) ightarrow ^4T_{2g}(F)$ ($v_1$), $^4A_{2g}(F) ightarrow ^4T_{1g}(F)$ ($v_2$) and $^4A_{2g}(F) ightarrow ^4T_{1g}(P)$ ($v_3$) in an octahedral geometry. The $v_2 / v_1$ ratio (1.31) also confirms the octahedral geometry for the complex. The 10 Dq, B and $\beta$ values were found to be 12228, 402 cm⁻¹ and 0.41 respectively. The lowering in the value of B from free ion for Cr(III) (1030 cm⁻¹) suggests high covalent nature (62%) of bonding.

The Fe(III) complex exhibits three bands at 11700, 19300 and 27000 cm⁻¹ which may be attributed to the transitions $^5A_{1g} ightarrow ^5T_{1g}(G)$ ($v_1$), $^5A_{1g} ightarrow ^5T_{2g}(G)$ ($v_2$) and $^5A_{1g} ightarrow ^5E_g(G)$ ($v_3$) respectively for octahedral complexes. The $v_2 / v_1$ ratio (1.7) was found to be 1.6, 10500 cm⁻¹, 700 cm⁻¹ and 0.51 respectively. These are in fair agreement with octahedral geometry for the Mn(II) complex. The lowering in the value of B from free ion for Mn(II) (960 cm⁻¹) suggests covalent (30.23%) nature of bonding.

In the IR spectra of the Cr(III) and Mn(II) complexes, one double hump at 3200-3500 cm⁻¹ and in the Fe(III) and Zn(II) complexes broad bands at 3300 cm⁻¹ followed by sharp peaks at ~1600, 830 cm⁻¹ assignable to OH stretching, bending and rocking vibrations respectively indicates the presence of coordinated water molecules in the complexes. The ligand bands at 3400 (NH) and 1575 cm⁻¹ (C=O) shifted by ±15-20 cm⁻¹ in the complexes, indicating the coordination through these groups. In the far IR region, the chelates show new medium intensity bands at 520-544 and 470-450 cm⁻¹ comparable with vM-O and vM-N respectively. In Mn(II) complex, additional bands at 1548, 1452, 1301 and 701 cm⁻¹ can be assigned to $v_{asym}$(COO), Sym (COO), δ(CH₃) and δ(COO) respectively indicating the presence of acetate ion in the coordination sphere.

**Antiinflammatory activity**
Antiinflammatory activity of the complexes were performed using a plethysmometer to measure carrageenan induced rat paw volume following the method of Winter et al. Adult male wister albino rats (90-125g) were fasted for 18h but with free access to water. Each treatment i.e. plain drug and complexes was administered at a dose of 100 mg/kg

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**Table 1—Characterization data of the complexes**

<table>
<thead>
<tr>
<th>Comp./Colour, m.p./°C</th>
<th>Mol.wt. found (calcd.)</th>
<th>M</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Cl</th>
<th>$\mu$ eff.</th>
<th>$\lambda_m$ cm⁻¹ mol⁻¹</th>
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<tr>
<td>[Cr(C₆H₆NO₂Cl)₂H₂O] Cl</td>
<td>711.57 (713.70)</td>
<td>7.08</td>
<td>47.96</td>
<td>3.46</td>
<td>3.98</td>
<td>24.62</td>
<td>3.87</td>
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<td>Light blue 125</td>
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<td></td>
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<tr>
<td>[Mn(C₆H₆NO₂Cl)₂]</td>
<td>464.67 (463.14)</td>
<td>11.49</td>
<td>41.95</td>
<td>4.07</td>
<td>3.15</td>
<td>15.01</td>
<td>5.86</td>
<td>7.00</td>
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<tr>
<td>CH₃COO·3H₂O Light brown 140</td>
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<tr>
<td>[Fe(C₆H₆NO₂Cl)₂OH·H₂O]</td>
<td>680.20 (681.12)</td>
<td>8.07</td>
<td>49.54</td>
<td>3.45</td>
<td>4.17</td>
<td>20.64</td>
<td>5.81</td>
<td>8.12</td>
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<td>Dark brown 180</td>
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<td></td>
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<tr>
<td>[Zn(C₆H₆NO₂Cl)₂H₂O] White 120</td>
<td>694.03 (691.67)</td>
<td>9.31</td>
<td>48.86</td>
<td>3.54</td>
<td>4.00</td>
<td>20.36</td>
<td>Diamagnetic</td>
<td>9.00</td>
</tr>
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</table>
equal doses, the Cr(III) and Zn(II) complexes are concomitantly, increasing the synthesis of
the cysteine (vasoconstrictor) PGF2α, following the addition of copper sulphate or chloride to seminal vesicle
homogenates. These results suggest that the mechanism action of Cr(III) and Zn(II) complexes may be, at least in part, at the level of the prostaglandin mediation of inflammation. This is to say, these complexes may play a role in decreasing the synthesis of the proinflammatory PGE2 and concomitantly, increasing the synthesis of the antiinflammatory PGF2α (Table 2).

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References
17. Willis A L, Personal communication.