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The influence of salt formation on electrostatic and compression properties of flurbiprofen salts

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### Table 1: Parent drug and selection of counterions used in this research.

<table>
<thead>
<tr>
<th>Parent drug</th>
<th>Acronym</th>
<th>Manufacturer</th>
<th>Chemical Formula</th>
<th>pKa</th>
<th>CLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurbiprofen</td>
<td>F</td>
<td>Aesica, UK</td>
<td>C₁₃H₁₃FO₂</td>
<td>4.4</td>
<td>3.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amines</th>
<th>Acronym</th>
<th>Manufacturer</th>
<th>Formula</th>
<th>pKa</th>
<th>CLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butylamine</td>
<td>But</td>
<td>Sigma Aldrich, USA</td>
<td>C₄H₉NH₂</td>
<td>10.3</td>
<td>0.92</td>
</tr>
<tr>
<td>Octylamine</td>
<td>Oct</td>
<td>Fluka, USA</td>
<td>C₆H₁₇NH₂</td>
<td>10.3</td>
<td>3.04</td>
</tr>
<tr>
<td>Benzylamine</td>
<td>Benz</td>
<td>Acros, USA</td>
<td>C₆H₃CH₂NH₂</td>
<td>9.4</td>
<td>1.09</td>
</tr>
<tr>
<td>Cyclo-hexylamine</td>
<td>C-hex</td>
<td>Lancaster, UK</td>
<td>C₆H₁₁NH₂</td>
<td>10.5</td>
<td>1.98</td>
</tr>
<tr>
<td>Tert-butylamine</td>
<td>T-but</td>
<td>Sigma Aldrich, USA</td>
<td>(CH₃)₃CNH₂</td>
<td>10.5</td>
<td>0.59</td>
</tr>
<tr>
<td>2-amino-2-methylpropan-1-ol</td>
<td>AMP1</td>
<td>Fluka, USA</td>
<td>C₄H₁₁NO</td>
<td>9.2</td>
<td>-0.59</td>
</tr>
<tr>
<td>Tris(hydroxymethyl)aminomethane</td>
<td>Tris</td>
<td>Sigma Aldrich, USA</td>
<td>(HOCH₂)₃CNH₂</td>
<td>6.4</td>
<td>-0.94</td>
</tr>
</tbody>
</table>

### Table 2: Classification on the basis of Heckel parameter, $P_y$ (Nordström et al., 2012).

<table>
<thead>
<tr>
<th>Heckle parameter, $P_y$</th>
<th>Characteristics of compacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 Mpa</td>
<td>Very soft</td>
</tr>
<tr>
<td>40 Mpa &lt; $P_y$ &lt; 80MPa</td>
<td>Soft</td>
</tr>
<tr>
<td>80 MPa &lt; $P_y$ &lt; 200MPa</td>
<td>Moderately hard</td>
</tr>
<tr>
<td>$P_y$ &gt; 200 MPa</td>
<td>Hard</td>
</tr>
</tbody>
</table>
**Table 3**: Physicochemical and mechanical properties of flurbiprofen and its salts.

<table>
<thead>
<tr>
<th></th>
<th>$Q_{\text{sat}}$ (nC/g)</th>
<th>Adhesion (%)</th>
<th>Density (g/cm$^3$)</th>
<th>$M_p$ (°C)</th>
<th>Solubility (mol/L)*</th>
<th>$d_{10}$ (µm)</th>
<th>$d_{50}$ (µm)</th>
<th>$d_{90}$ (µm)</th>
<th>Particle Shape</th>
<th>$b^{1/2}$ (MPa)</th>
<th>$P_y$ (MPa)</th>
<th>Compact characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBP</td>
<td>-226</td>
<td>46</td>
<td>1.315</td>
<td>115</td>
<td>7.72x10$^{-4}$</td>
<td>8</td>
<td>20</td>
<td>43</td>
<td>Equant</td>
<td>7.9 (1.4)</td>
<td>70.2 (2.6)</td>
<td>Soft</td>
</tr>
<tr>
<td>F-But</td>
<td>-17</td>
<td>12</td>
<td>1.199</td>
<td>146</td>
<td>0.0489</td>
<td>8</td>
<td>40</td>
<td>190</td>
<td>Prism</td>
<td>7.5 (1.2)</td>
<td>84.1 (1.9)</td>
<td>Moderately hard</td>
</tr>
<tr>
<td>F-Oct</td>
<td>-18</td>
<td>15</td>
<td>1.129</td>
<td>102</td>
<td>3.69x10$^{-3}$</td>
<td>11</td>
<td>28</td>
<td>61</td>
<td>Tabular</td>
<td>8.2 (0.8)</td>
<td>110.6 (2.3)</td>
<td>Moderately hard</td>
</tr>
<tr>
<td>F-Benz</td>
<td>-75</td>
<td>16</td>
<td>1.237</td>
<td>136</td>
<td>8.01x10$^{-3}$</td>
<td>24</td>
<td>128</td>
<td>265</td>
<td>Needle</td>
<td>8.1 (0.9)</td>
<td>91.2 (1.0)</td>
<td>Moderately hard</td>
</tr>
<tr>
<td>F-Chex</td>
<td>+31</td>
<td>12</td>
<td>1.229</td>
<td>209</td>
<td>0.0126</td>
<td>9</td>
<td>57</td>
<td>132</td>
<td>Needle</td>
<td>8.3 (0.5)</td>
<td>114.4 (1.4)</td>
<td>Moderately hard</td>
</tr>
<tr>
<td>F-Tbut</td>
<td>+7</td>
<td>6</td>
<td>1.240</td>
<td>184</td>
<td>0.0435</td>
<td>9</td>
<td>65</td>
<td>149</td>
<td>Needle</td>
<td>7.4 (0.5)</td>
<td>62.91 (1.4)</td>
<td>Soft</td>
</tr>
<tr>
<td>F-AMP1</td>
<td>-350</td>
<td>32</td>
<td>1.319</td>
<td>154</td>
<td>0.199</td>
<td>8</td>
<td>95</td>
<td>194</td>
<td>Needle</td>
<td>13.0 (0.1)</td>
<td>228.0 (1.2)</td>
<td>Hard</td>
</tr>
<tr>
<td>F-Tris</td>
<td>-70</td>
<td>25</td>
<td>1.424</td>
<td>152</td>
<td>0.248</td>
<td>13</td>
<td>102</td>
<td>189</td>
<td>Columnar</td>
<td>13.5 (0.7)</td>
<td>242.0 (2.8)</td>
<td>Hard</td>
</tr>
</tbody>
</table>

$Q_{\text{sat}}$: Electrostatic charge at saturation point  
$M_p$: Melting point  
$P_y$: Mean yield pressure (Heckel parameter)  

* Pressure required to reduce the powder bed to 50% (Kawakita parameter)  
* Aqueous solubility data (David *et al.*, 2012)
Table 4: Unit cell dimensions, intermolecular distances and intermolecular angles for F-Tbut, F-AMP1 and F-Tris salts (Schwalbe et al., 2010).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F-Tbut</th>
<th>F-AMP1</th>
<th>F-Tris</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a$ /Å</td>
<td>15.9343</td>
<td>16.1330</td>
<td>6.1930</td>
</tr>
<tr>
<td>$b$ /Å</td>
<td>6.2903</td>
<td>6.2700</td>
<td>9.9421</td>
</tr>
<tr>
<td>$c$ /Å</td>
<td>19.1949</td>
<td>18.8520</td>
<td>14.6846</td>
</tr>
<tr>
<td>$\alpha$ deg</td>
<td>90.0</td>
<td>90.0</td>
<td>93.94</td>
</tr>
<tr>
<td>$\beta$ deg</td>
<td>114.7</td>
<td>114.7</td>
<td>90.03</td>
</tr>
<tr>
<td>$\gamma$ deg</td>
<td>90.0</td>
<td>90.0</td>
<td>90.72</td>
</tr>
</tbody>
</table>

Intermolecular distances / Å

<table>
<thead>
<tr>
<th></th>
<th>F-Tbut</th>
<th>F-AMP1</th>
<th>F-Tris</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1 – H1B</td>
<td>1.869</td>
<td>1.880</td>
<td>3.158</td>
</tr>
<tr>
<td>O1 – H1A</td>
<td>1.863</td>
<td>1.856</td>
<td>1.924</td>
</tr>
<tr>
<td>O1 – H4</td>
<td>7.107</td>
<td>7.007</td>
<td>1.795</td>
</tr>
<tr>
<td>O2 – H1C</td>
<td>1.882</td>
<td>1.888</td>
<td>1.922</td>
</tr>
<tr>
<td>O1 – N1</td>
<td>2.767</td>
<td>2.760</td>
<td>2.771</td>
</tr>
<tr>
<td>O2 – N1</td>
<td>2.790</td>
<td>2.797</td>
<td>2.809</td>
</tr>
<tr>
<td>O2 – O3</td>
<td>-</td>
<td>4.002</td>
<td>2.692</td>
</tr>
<tr>
<td>O3 – H3F</td>
<td>-</td>
<td>2.022</td>
<td>3.480</td>
</tr>
<tr>
<td>F1 – F2</td>
<td>2.515</td>
<td>2.587</td>
<td>6.307</td>
</tr>
<tr>
<td>F1 – H8</td>
<td>2.675</td>
<td>2.688</td>
<td>3.166</td>
</tr>
<tr>
<td>F1 – H18</td>
<td>2.940</td>
<td>2.820</td>
<td>2.761</td>
</tr>
<tr>
<td>F2 – H11</td>
<td>2.445</td>
<td>2.398</td>
<td>2.463</td>
</tr>
</tbody>
</table>

Intermolecular angles / deg

<table>
<thead>
<tr>
<th></th>
<th>F-Tbut</th>
<th>F-AMP1</th>
<th>F-Tris</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 – O1 - C</td>
<td>127.993</td>
<td>130.988</td>
<td>31.261</td>
</tr>
<tr>
<td>O2 – O1 – N1</td>
<td>108.024</td>
<td>111.195</td>
<td>48.167</td>
</tr>
</tbody>
</table>