PRELIMINARY COMPARISON OF INTERPARTICULATE ADHESION MEASURED BY
ATOMIC FORCE MICROSCOPY & CALCULATED FROM HANSEN
SOLUBILITY PARAMETERS MEASURED BY INVERSE GAS CHROMATOGRAPHY

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1. Introduction

– The relationship between particle-particle interactions & dry powder inhaler (DPI) fine particle fraction (FPF) has been the subject of much recent research.
– One approach that has proved successful is the measurement of cohesive-adhesive balance (CAB) ratios between drugs & excipients using atomic force microscopy (AFM) (1, 2, 3).
– A CAB ratio describes the cohesion between the particles of one material relative to its adhesion to another material. Such ratios have demonstrated a consistent relationship with DPI FPF (3).
– Another technique that has been widely studied is inverse gas chromatography (IGC). In the majority of this work, dispersive surface energy was measured, with mixed results.
– Tong et al. employed another IGC approach, by measuring Hansen solubility parameters, from which the strength of the various adhesive & cohesive interactions within in a formulation could be calculated (4).
– Subsequently, these data were found to relate to the in vitro performance of DPI formulations (4).
– The aim of this study was to compare the data produced by these two techniques, which, in theory, should follow the same trends.

2. Atomic force microscopy

– The CAB ratios between five model micronised drugs & three model 63-90 µm sieved excipients were measured using the standard CAB technique (1, 2).

Table 1: AFM CAB ratios for the interaction of each drug with each excipient. \( R^2 > 0.91 \) in each case.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Erythritol</th>
<th>Lactose</th>
<th>Mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becloometasone dipropionate (BDP)</td>
<td>0.51 ± 0.05</td>
<td>0.74 ± 0.04</td>
<td>0.69 ± 0.05</td>
</tr>
<tr>
<td>Budesonide</td>
<td>1.38 ± 0.01</td>
<td>0.91 ± 0.03</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td>Salbutamol sulphate</td>
<td>1.03 ± 0.05</td>
<td>0.72 ± 0.02</td>
<td>1.04 ± 0.03</td>
</tr>
<tr>
<td>Terbutaline sulphate</td>
<td>1.09 ± 0.03</td>
<td>0.72 ± 0.03</td>
<td>0.98 ± 0.03</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>1.15 ± 0.03</td>
<td>0.89 ± 0.03</td>
<td>0.96 ± 0.02</td>
</tr>
</tbody>
</table>

3. Inverse gas chromatography

– Hansen solubility parameters determined by IGC following the method described by Tong et al. (4).
– Adhesive & cohesive interactions between the materials calculated from their solubility parameters using the calculations described by Rowe (5). These were used to calculate IGC CAB ratios.

Table 2: Theoretical IGC CAB ratios for the interaction of each drug with each excipient.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Erythritol</th>
<th>Lactose</th>
<th>Mannitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becloometasone dipropionate (BDP)</td>
<td>1.33</td>
<td>0.98</td>
<td>1.18</td>
</tr>
<tr>
<td>Budesonide</td>
<td>1.44</td>
<td>1.02</td>
<td>1.28</td>
</tr>
<tr>
<td>Salbutamol sulphate</td>
<td>1.31</td>
<td>0.95</td>
<td>1.17</td>
</tr>
<tr>
<td>Terbutaline sulphate</td>
<td>14.00</td>
<td>6.14</td>
<td>12.45</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>2.41</td>
<td>1.31</td>
<td>2.21</td>
</tr>
</tbody>
</table>

4. Comparison of AFM & IGC CAB ratios

– Considering all the data, there was no correlation between the two sets of CAB ratios.
– If each drug is considered separately, there was a stronger correlation (\( R^2 \geq 0.67 \) in each case).
– However, the BDP line of best fit had a negative gradient.
– Therefore, the IGC technique may be able to produce CAB ratios of the same rank order as AFM for certain drugs.

5. Further work

– A study of the in vitro performance of carrier-based DPI formulations produced using the study materials will examine which technique (AFM or IGC) is most predictive of FPF.
– The reason for the negative AFM-IGC CAB ratio relationship for BDP will be investigated.

6. References


7. Acknowledgements

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