Dry heat stress stability of model peptide: buserelin

Matthias D’Hondt and Bart De Spiegeleer*
Drug Quality and Registration (DruQuaR) group, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, B-9000 Ghent, Belgium.

* Corresponding author: bart.despiegeleer@ugent.be (O. Ref.: 2012-182c)

INTRODUCTION
Recently, the pharmaceutical industry showed a renewed interest in therapeutic peptides. Depending on the therapeutic application, processing of therapeutic peptides into controlled release implants would result in a patient friendly, long-term treatment. Hot melt extrusion (HME) is a fast and cost-efficient processing technique with 3 critical aspects: high temperature exposure during short time periods, mechanical shear stress influence and polymer/matrix influence. Buserelin, an gonadotropin hormone releasing agonist peptide implemented in the treatment of prostate cancer, was subjected in its dry powder state to short-term heat exposure to evaluate the first critical HME aspect [1].

EXPERIMENTAL

Dry heat conditions

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>150</th>
<th>157.5</th>
<th>165</th>
<th>172.5</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>40</td>
<td>25</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>80</td>
<td>50</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>120</td>
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<td>45</td>
<td>30</td>
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<tr>
<td>160</td>
<td>100</td>
<td>60</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Data evaluation
- Calculate degradation constant k at each temperature, assuming first order kinetics
- Derive Eₐ from Arrhenius equation
- Identify degradants using LCQ IonTrap MS

RESULTS and DISCUSSION

CONCLUSIONS
The activation energy of buserelin was estimated to be 216.8 and 87.0 kJ/mol in dry and molten state, resp. Therefore, buserelin is a valid candidate for hot melt extrusion processing. Moreover, new low melting polymers, i.e. <100 °C, and short HME exposure time, i.e. 5 minutes, should limit the thermal stress on the peptide API.

The structures of a number of buserelin degradants were identified using mass spectrometry.

REFERENCES