Hyaluronic Acid, a new recombinant Controlled Release Excipient for Oral Solid Dosage Forms

Ole M. Dall¹, Khadija Schwach-Abdellaoui¹ and Mette-Marie L. Jensen¹

¹Novozymes Biopharma DK A/S, Bagsvaerd, DK-2880, Denmark
omad@novozymes.com

ABSTRACT SUMMARY
Hyaluronic acid (HA) from Bacillus subtilis was tested as an oral solid dose excipient for controlled drug release. Release studies show a significant increase in drug release time when HA was added to tablets containing tramadol hydrochloride. A correlation between the added amount of HA and the specific release time of tramadol was identified.

INTRODUCTION
Oral solid dosage forms are the most common way of administrating orally absorbed pharmaceuticals. The oral route has been the preferable route of administration especially of analgesics in the treatment of symptoms related to pain, because the treatment is mainly patient controlled. A reduction in the number of daily drug administrations is highly desirable, to improve the specific patient compliance and the entire disease treatment in general. Compounds and excipients with controlled release properties are well known and often used in oral administrated formulations like tablets and capsules in order to provide a well-defined and stable release of the active substance during the passage through the gastro intestinal tract. HA has a special property of forming a gel-like coating around the solid drug particles and therefore slow down the dissolving rate of the drug. This will slow down the absorption in the intestinal tract into systemic circulation. To utilize these special properties of HA in solid oral dosage forms, the formulation must be protected from the acidic environment in the stomach (pH 1-2). HA exposed to a pH level below 4-5 will lead to acid facilitated depolymerization and loss of the gel forming properties. A tablet formulation can be coated with a gastro resistant material like an acrylate copolymer (Eudragit®) to ensure safe passage through the stomach and initiate release of the active compound in the intestinal tract (Duodenum, jejunum and ileum, pH 5.5–7.5)¹.

Hyaluronic acid is a natural linear and unbranched polysaccharide belonging to the class of non-sulphated glycosaminoglycans. HA is composed of beta-1,3-N-acetyl glucosamine and beta-1,4-glucuronic acid repeating disaccharide units² (figure 1).

Figure 1: Chemical structure of the repeating disaccharide unit in HA.

Hyaluronosaccharides are produced in the body from hyaluronidase, a new HA is a novel and superior Bacillus subtilis-derived HA produced according to Q7 cGMP and specifically targeted towards pharmaceutical applications including oral solid dosage forms.

Tramadol hydrochloride is a centrally-acting analgesic, used in treating moderate to moderately severe pain. It is a synthetic analog of the phenanthrene alkaloid codeine and, as such, is an opioid and also a pro-drug (codeine is metabolized to morphine in the body). Tramadol (figure 2) has a wide range of other applications, including treatment for restless leg syndrome, acid reflux, and fibromyalgia. The compound is primarily absorbed in the small intestinal tract and is commonly used in oral formulations.

Figure 2: Chemical structure of R/S tramadol

EXPERIMENTAL METHODS
The tablets were prepared by direct compression of a dry granulated mixture of the API, various amounts of HA (0-4 % w/w) and several other excipients. The dimensions were Ø 10 mm, 4 mm in height and with a slight convex shape. The dose of tramadol hydrochloride was 100 mg and the total tablet mass was 400 mg.

The composition of the tablets was (mg per tablet): HA 850 kDa (4-16), tramadol hydrochloride (100), microcrystalline cellulose (210), anhydrous lactose (50), polyvinylpyrrolidone (22), hydroxypropyl cellulose (8), colloidal silicon dioxide (4), magnesium stearate (2). The prepared tablets had an average hardness of 270 ± 30 N and a disintegration time in the range of 50 to 120 minutes.

The release of tramadol from the uncoated tablets was assessed by dissolution analysis using a closed loop system configuration (SOTAX CE7smart) and USP 4 dissolution method with 22.4 mm dissolution cells. 250 mL of a 200 mM PBS buffer at pH 6.8 was used as dissolution medium and the system was equilibrated at 37 °C. The flow rate was 8 mL/min and a high stirring speed was used. Tramadol was detected on-line with UV absorbance at 270 nm. One tablet containing 100 mg tramadol was loaded into each of a total of seven test cells.
RESULTS AND DISCUSSION

The dissolution profiles of uncoated tablets containing tramadol hydrochloride and HA as controlled release agent (figure 3 and 4) shows that HA has controlled release properties when added to a tablet formulation. A tablet without HA added, will release 95 % of the active substance within 1.9 hours (Table 1). When HA is added as a solid powder into the tablet granules before compacting, the release time of tramadol hydrochloride will increase gradually up to 7.5 hours with the highest HA concentration tested of hen 4 % (table 1).

Table 1: Release time (95%) of tramadol from the tablets.

<table>
<thead>
<tr>
<th>Amount of HA in tablet (% w/w)</th>
<th>Tramadol release time (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.9</td>
</tr>
<tr>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>1.0</td>
<td>2.9</td>
</tr>
<tr>
<td>1.5</td>
<td>3.6</td>
</tr>
<tr>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td>4.0</td>
<td>7.5</td>
</tr>
</tbody>
</table>

The tested tablets were not coated with an acid resistant coating because applied dissolution method was not designed to mimic the acidic conditions in the stomach. If this formulation should be clinically tested, the HA containing tablet will have to be coated to protect HA from acidic degradation and ensure drug release after stomach passage.

CONCLUSION

It can be concluded that by adding bacillus-derived HA into a tablet containing tramadol hydrochloride for oral administration, the release of tramadol hydrochloride can be prolonged from 1.9 to 7.5 hours. A good correlation has been identified between the added amounts of HA and the drug release time. This correlation gives excellent possibilities for developing specific drug release profiles for different oral drug applications.

REFERENCES