Intravaginal drug delivery

The vagina offers numerous advantages as a site for drug delivery, such as easy access, prolonged retention of formulations, a great permeation area, high vascularisation, relative low enzymatic activity and the avoidance of first-pass metabolism. Intravaginal administration of drugs, which are specifically used for the treatment of osteoporosis, hormone replacement therapy, contraception, infections, infertility and other female related conditions, is a feasible alternative to parenteral or oral administration. In Fig. 1 the anatomy of the female reproductive tract is illustrated.

For intravaginal drug delivery thiomers offer the advantage of high in situ gelling, mucoadhesive, controlled release and enzyme inhibitory properties leading to a strongly improved therapeutic potential of numerous drugs [1].

In situ gelation

Various polymers are capable of prolonging the residence time of drug delivery systems by their in situ gelling properties. In comparison to so far used in situ gelling polymers, thiolated polymers are capable of providing a comparatively more pronounced increase in viscosity after application, as an extensive crosslinking process by the formation of disulfide bonds between the polymer chains—as illustrated in Fig. 2—takes place. For instance, in case of thiolated chitosan a more than 1000-fold increase in viscosity by the formation of disulfide bonds within the polymeric network based on a simple oxidation process was shown [2]. In Fig. 3 the increase in viscosity due to disulfide bond formation is illustrated. Being applied in liquid form, they become highly viscous gels in the vagina, which avoids an unintended elimination and outflow of the semisolid delivery system. In Fig. 4 this increase in viscosity is illustrated.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Adhesion time in hours; mean ± SD (n=3-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiolated Chitosan</td>
<td>161 ± 7.2</td>
</tr>
<tr>
<td>Thiolated Polycarbophil</td>
<td>26.0 ± 0.9</td>
</tr>
<tr>
<td>Thiolated Poly(Acrylic Acid)</td>
<td>19.4 ± 0.8</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>15.2 ± 0.4</td>
</tr>
<tr>
<td>Carbopol 980</td>
<td>12.5 ± 0.9</td>
</tr>
<tr>
<td>Carbopol 974</td>
<td>10.3 ± 0.9</td>
</tr>
<tr>
<td>Polyactarbulphil</td>
<td>10.2 ± 0.8</td>
</tr>
<tr>
<td>Carbopol 960</td>
<td>9.8 ± 0.2</td>
</tr>
</tbody>
</table>

Controlled drug release

Due to a sustained drug release, a prolonged therapeutic level can be guaranteed in the vagina. Consequently the frequency of dosing can be reduced contributing to an improved compliance. The release of drugs out of thiomier carrier systems can be controlled by a simple diffusion process and/or
ion interactions [7]. Hence, a controlled drug release for numerous days and even for weeks can be guaranteed. A comparison of the release behaviour of a model drug (progesterone) out of various polymers utilized as carrier matrix is provided in Fig. 6.

**Enzyme inhibition**

Many non-invasively administered drugs such as therapeutic peptides are degraded on the vaginal mucosa by membrane bound enzymes strongly reducing their systemic bioavailability [9]. Because of their capability to bind Zn$^{2+}$ ions via thiol groups, thiomers are potent inhibitors of most membrane bound zinc-dependent enzymes. Due to this enzyme inhibitory effect, thiomers can significantly improve the bioavailability of intravaginally administered drugs.

Thiomer formulations can be intravaginally administered in form of:
- liquids
- gels
- tablets
- capsules

Once applied they remain on the vaginal mucosa even for weeks guaranteeing a controlled drug release over the intended time period.

**Scaled-up production / GMP material**

The production capacity for certain thiomers is already in the range of several 100 kg per year and can be further 10-100-fold scaled-up within a year on demand. Moreover for certain thiomers GMP material is available.

**Partnering opportunity**

The thiomer-technology is worldwide protected by various patents. ThioMatrix offers the thiomer-technology for licensing to third parties on a product-by-product basis.

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**References**


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**Fig. 5.** Formation of disulfide bonds between thiomers and the mucus gel layer

**Fig. 6.** Release profiles of progesterone from tablets based on microcrystalline cellulose (Eicema) (--) and thiolated crosslinked poly(acrylic acid) (--• --• --•). Studies were carried out in 100 mM phosphate buffered saline, pH 6.0. Adapted from Valenta et al. [8].

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**For more information**

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