Thiomers – Potent Auxiliary Agents in Intravaginal Drug Delivery

ThioMatrix

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.

Technology Snapshot:

Strongly prolonged vaginal residence time

In situ gelling properties

Sustained drug release

Worldwide patent protection

Mucoadhesion

In contrast to 'conventional' polymers, whose mucoadhesive properties are exclusively based on non-covalent bonds, thiolated polymers or designated thiomers are capable of forming covalent bonds with cysteine-rich subdomains of the mucus gel layer as illustrated in Fig. 5. The bridging structure most commonly utilized in biological systems -namely the disulfide bond- is thereby used.

Due to the immobilization of thiol groups the mucoadhesive properties of chitosan and poly(acrylic acid), for instance, are improved at least 140-fold [3] and 20-fold [4], respectively. In Table 1 the rank order of the most mucoadhesive polymers tested via the rotating cylinder method is provided [5]. The mucoadhesive properties of drug delivery systems based on thiomers were also demonstrated in human volunteers [e.g. 6].

Table 1. *Rank order of most mucoadhesive polymers. Adapted from Grabovac et al. [3]*

Polymer	Adhesion time in hours; means ± SD (n = 3–5)
Thiolated Chitosan	161.2 ± 7.2
Thiolated Polycarbophil	26.0 ± 0.9
Thiolated Poly(Acrylic Acid)	19.4 ± 0.8
Hydroxypropylcellulose	15.2 ± 0.4
Carbopol 980	12.5 ± 0.9
Carbopol 974	10.3 ± 0.9
Polycarbophil	10.2 ± 0.8
Carbopol 980	9.8 ± 0.2

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 thiomer carrier systems can be controlled by a simple diffusion process and/or

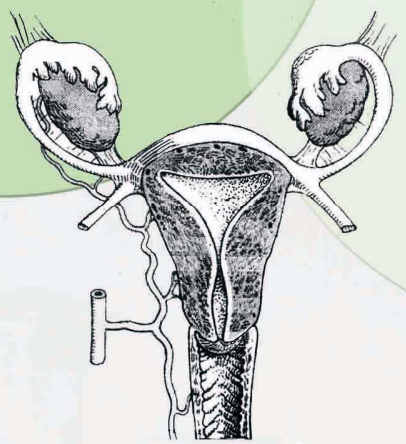

Fig. 1. *Schematic presentation of the anatomy of the female reproductive tract*

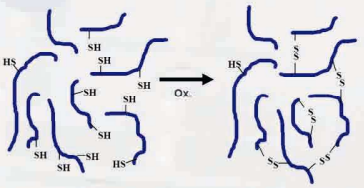

Fig. 2. *Crosslinking process of thiomers due to oxidation*

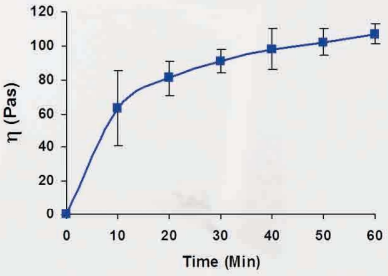

Fig. 3. *Increase in viscosity of an aqueous 3% (m/v) thiolated chitosan solution pH 6.4 in the presence of oxygen as a function of time.*

Fig. 4. *Left hand side 1% thiolated poly(acrylic acid) solution before oxidation and right hand side after oxidation*

ionic 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- up to 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.

References

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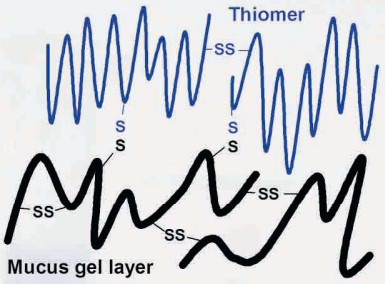

Fig. 5. *Formation of disulfide bonds between thiomers and the mucus gel layer*

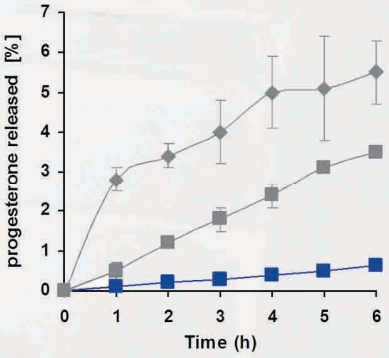

Fig. 6. *Release profiles of progesterone from tablets based on microcrystalline cellulose (Elcema) (–♦–), crosslinked poly(acrylic acid) (–■–) and thiolated crosslinked poly(acrylic acid) (–■–). Studies were carried out in 100 mM phosphate buffered saline, pH 6.0. Adapted from Valenta et al. [8].*

For more information

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