Thiomers – A Novel Generation of Polymeric Efflux Pump Inhibitors

ThioMatrix

Inhibition of efflux pumps

The oral bioavailability of numerous drugs as listed in Table 1 is significantly reduced due to efflux pumps. In addition efflux pumps are responsible for high variability in drug uptake.

High efflux pump inhibitory potential

Thiomers are among the most potent polymeric efflux pump inhibitors currently available [1-4]. They show, for instance, a 2.7-fold higher effect in vivo than PEGs and PEG derivatives such as Pluronic P85 [5]. In Fig. 1-3 examples for the improved oral bioavailability of various efflux pump substrates due to the co-administration of thiomers is shown [6-8]. Futhermore, the potential of thiomers as efflux pump inhibitors was shown via a significant reduction in the tumor growth in rats after oral administration of paclitaxel with a thiomer [9].

Mode of action

The postulated mechanism of efflux pump inhibition is based on an interaction of thiomers with the channel forming transmembrane domain of various efflux pumps such as P-gp and multidrug resistance proteins (MRPs). P-gp, for instance, exhibits 12 transmembrane regions forming a channel through which substrates are transported outside of the cell. Two of these transmembrane domains – namely 2 and 11 – exhibit on position 137 and 956, respectively, a cysteine subunit. Thiomers seem to enter in the channel of P-gp and likely form subsequently one or two disulfide bonds with one or both cysteine subunits located within the channel. Due to this covalent interaction the allosteric change of the transporter being essential to move drugs outside of the cell might be blocked [10]. The postulated mechanism is illustrated in Fig. 4.

Technology Snapshot:

Non-absorbable efflux pump inhibitors
100% reversible efflux pump inhibition
Strongly improved bioavailability
Worldwide patent protection

Table 1. *Classes of drugs being substrates of efflux pumps.*

Class	Representatives
antibiotics	erythromycin actinomycin mitomycin ampicillin cloxacillin clarithromycin azithromycin ciprofloxacin grepafloxacin
antiinflammatory drugs	prednisolone piroxicam indomethacin flurbiprofen diclofenac naproxen ibuprofen
chemotherapeutics	paclitaxel docetaxel doxorubicin cisplatin daunorubicin vinblastine
antiviral drugs	saquinavir amprenavir indinavir ritonavir nelfinavir acyclovir lopinavir
antimycotics	griseofulvin itraconazole astemizole ketoconazole miconazol clotrimazol
immunosuppressive drugs	tacrolimus sirolimus cyclosporine
peptide and protein drugs	cyclosporine octreotide leu-enkephalin
statins	atorvastatin pravastatin
hormones	progesterone estrogen
antiarrhythmics	amiodarone
analgetic drugs	morphines
calcium channel inhibitors	nifedipine

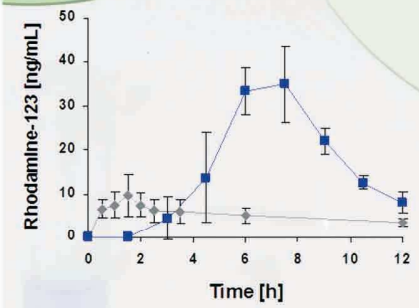

Fig. 1. *PK of rhodamine 123 having been administered with (■) and without (♦) a thiomer. Adapted from Föger, F. et al. [6].*

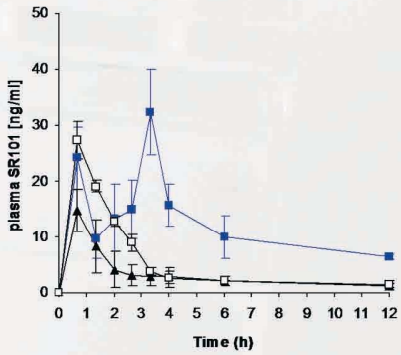

Fig. 2. *Plasma curves of sulforhodamine (S-Rho) after oral administration of 1.5 mg sulforhodamine in solution (▲), in solution with poly(acrylic acid) (□) or in solution with thiolated poly(acrylic acid) (■). Adapted from Greindl et al. [7].*

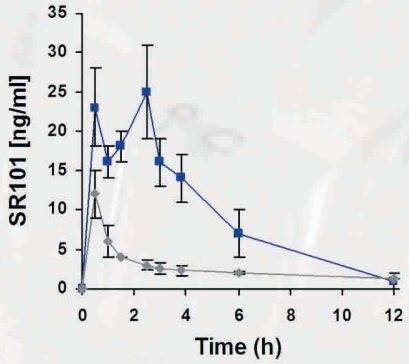

Fig. 3. *Plasma curves of different SR101 solutions (ng/ml) after oral administration of 1.5 mg SR101 with 20 mg of thiolated alginate (■) and with buffer only (♦). Adapted from Palmberger et al. [8].*

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 10- up to 100-fold further scaled-up within a year on demand. Moreover, for certain thiomers GMP material is available.

Safety and clinical data

In comparison to most other efflux pump inhibitors thiomers offer the advantage of

- not being absorbed from mucosal membranes

  Due to their high molecular mass thiomers are not absorbed from mucosal membranes. Hence systemic toxic side effects can be excluded. Furthermore, as certain thiomers such as thiolated chitosans are degraded in the colon, efflux pump inhibition takes place exclusively in the small intestine and is limited just to the time period of drug uptake.

- 100% reversible inhibition of efflux pumps

  In contrast to other efflux pump inhibitors (see Tab. 2) the inhibitory effect of thiomers is completely reversible.

Table 2. *Comparison of different efflux pump inhibitors in their mode of action.*

Mode of action	Type of inhibitor
reversible	Thiomers verapamil
non-reversible	Pluronic P85 6-mercaptopurine glutathione Myrj 52

Various biological safety reports are available. Furthermore, thiomers have already been tested in human volunteers showing neither damage nor any irritation of as sensitive mucosal membranes as the ocular epithelium [11].

Partnering opportunity

The thiomer-technology and in addition the efflux pump inhibitory properties of thiomers are 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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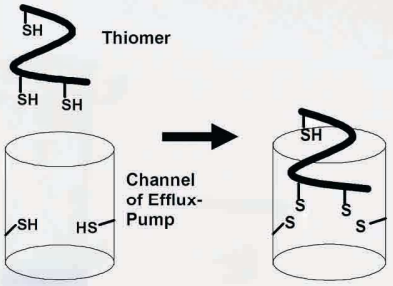

Fig. 4. *Postulated mechanism being responsible for efflux pump inhibition. Adapted from Bernkop-Schnürch and Grabovac [10].*

For more information

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