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## **Thiomers: Forms, Features and Formulations**

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### **ABSTRACT**

*Thiolated polymers or so called thiomers are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. These are generated by the immobilization of sulphhydryl-bearing compounds on the backbone of well established mucoadhesive polymeric excipients, such as chitosan and poly (acrylates). This functionalisation leads to significantly improved properties compared with the corresponding unmodified polymers. It has been demonstrated in various studies, that thiomers exhibit mucoadhesive, permeation enhancing, controlled release as well as enzyme and efflux pump inhibitory properties. Thiomers can be directly compressed to tablets or given as solutions. Furthermore thioimer based micro- and nanoparticles have already been developed. The forms, features and formulations of thiomers are summarized in this review.*

**Keywords:** thiomers, cationic, mucoadhesion, ocular inserts, nucleic acid delivery.

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### **INTRODUCTION**

In the recent years thiomers have been introduced as a promising tool in the field of mucoadhesive drug delivery. Generated by the immobilization of sulphhydryl bearing compounds on the polymeric backbone, thiomers display significantly increased mucoadhesive properties as a result of a covalent attachment to mucus glycoproteins. Strong cohesive properties obtained by the formation of inter- and intramolecular disulfide bonds result in comparatively higher stability leading to prolonged disintegration times and sustained drug release from tablets, micro particles and gels. Thiomers seem to be a valuable tool for the non invasive delivery of peptide and protein drugs. The efficacy of thioimer based drug delivery systems have been confirmed in various invivo studies [1, 2].

**Forms [3, 4]:**

**Cationic thiomers:** Cationic thiomers are mainly based on chitosans. The primary amino group at the 2-position of the glucosamine subunits of this polymer is the main target for the immobilization of thiol groups. Eg: chitosan–cysteine, chitosan–thiobutylamidine, chitosan–thioglycolic acid.

**Anionic thiomers:** Anionic thiolated polymers exhibit all carboxylic acid groups as anionic substructures. These carboxylic acid groups also offer the advantage that sulfhydryl moieties can be easily attached to such polymers via the formation of amide bonds. Eg: poly (acrylic acid)–cysteine, poly (acrylic acid)–cysteamine, carboxymethylcellulose–cysteine, alginate–cysteine.

**Features:**

**Mucoadhesion:** In contrast to conventional polymers whose mucoadhesive properties are exclusively based on non-covalent bonds, thiolated polymers are capable of forming covalent bonds with cysteine-rich sub-domains of the mucus gel layer. The bridging structure most commonly utilized in biological systems namely the disulfide bond is thereby used. Due to immobilization of thiol groups the mucoadhesive properties of chitosan and poly (acrylic acid) are improved at least 140 fold and 20 fold respectively [5,6]. The mucoadhesive properties of drug delivery systems based on thiomers were also demonstrated in human volunteers.

**Permeation enhancement:** Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the paracellular uptake of drugs [7]. In comparison to most low molecular weight permeation enhancers, thiolated polymers offer the advantage of not being absorbed from the mucosal membrane. Hence their permeation enhancing effect can be maintained for a comparatively longer period of time and systemic toxic side effects of the auxiliary agent can be excluded.

The likely mechanism responsible for this improved permeation enhancement has been attributed to the inhibition of the protein, tyrosine phosphatase which seems to be involved in the opening and closing process of the tight junctions [8]. As this permeation enhancing mechanism differs from most conventionally used permeation enhancers, the effect can be further improved by the combination of both types of permeation enhancing systems.

**Efflux pump inhibition [9, 10]:** Thiomers are able to reversibly inhibit efflux pumps. Because of this property the mucosal uptake of various efflux pump substrates such as anticancer drugs, antimycotic drugs and anti inflammatory drugs can be tremendously improved. Thiomers are among the most potent polymeric efflux pump inhibitors currently available. They show, for instance, a 2.7 fold higher effect *in vivo* than PEGs and PEG derivatives such as Pluronic P85.

Werle and Hoffer revealed efflux pump inhibitory capability of thiomers. Transmucosal transport of the P-gp substrate rhodamine 123 was strongly improved in the presence of thiolated chitosan. Foger *et al* showed that the oral bioavailability of rhodamine 123 is even 3-fold improved when this model P-gp substrate is embedded in thiolated chitosan minitablets given orally to rats. In addition, they reported that the inhibitory effect of thiomers is strongly dependent on their molecular mass. The postulated mechanism of efflux pump inhibition is based on an interaction

of thiomers with the channel forming transmembrane domain of efflux pumps such as P-gp and multidrug resistance proteins (MRPs).

**Enzyme inhibition** [11]: Many non-invasively administered drugs such as therapeutic peptides or nucleic acids are degraded on the mucosa by membrane bound enzymes strongly reducing their bioavailability. Because of their capability to bind  $ZN^{2+}$  ions via thiol groups, thiomers are potent inhibitors of most membrane bound and secreted zinc dependent enzymes. Due to this enzyme inhibitory effect, thiomers can significantly improve the bioavailability of non-invasively administered drugs.

A study was carried out to evaluate the potential of polycarbophil cysteine conjugates (PCP-Cys) as an oral excipient to protect leucine enkephalin from enzymatic degradation by the intestinal mucosa. Inhibitory activity was tested towards isolated amino peptidase N and excised intact pig intestinal mucosa with native mucus. Analytical results showed that PCP-cys had a significantly greater inhibitory effect than PCP on the amino peptidase N activity towards both substrates. PCP-Cys completely protected leu-enkp against amino peptidase N activity over a 2 h incubation period, whereas  $83 \pm 4$  and  $60 \pm 7\%$  remained stable in the presence of PCP & buffer only respectively. Thus thiolation of PCP increased the stability of Leu-enkp against enzymatic degradation by amino peptidase N and the intact intestinal mucosa.

**In situ Gelation:** Rapid clearance from the site of drug action is one important factor that limits the efficacy of drugs administered to the ocular, nasal and vaginal mucosa. It is widely accepted that limiting the clearance by increasing the viscosity of a drug formulation will result in an increased bioavailability of these drugs. In situ gel formation is a promising strategy to obtain drug formulations of sufficient viscosity. The formation of gel at the site of drug delivery combines the advantages of a solution, which can be easily administered, with the favorable viscoelastic properties of a gel [8]. Thiolated chitosan were synthesized and studied for its various properties by Sreenivas S.A et al. They reported that thiolated chitosans displayed in situ gelling properties due to the oxidization of thiol groups at physiological pH values which results in the formation of inter and intramolecular disulfide bonds. This crosslinking process was observed within a pH range of 5 - 6.8. Also the rheologic properties of an in situ crosslinking thiolated deacetylated gellan gum (DGG) were examined invitro. The thiolated polymers was found to be capable of forming inter and / or intramolecular disulfide bonds in aqua solution at pH7 [12].

**Matrices for controlled drug release:** Due to a sustained drug release a prolonged therapeutic level can be guaranteed. Consequently the frequency of dosing can be reduced contributing to an improved compliance. The release of drugs out of polymeric carrier systems can be controlled by a simple diffusion process and/or ionic interactions. The cohesion and stability of a drug delivery system over the intended duration of drug liberation is often a substantial requirement for a controlled release. Thiolated chitosans besides their strong mucoadhesive and permeation enhancing properties also display excellent cohesive properties. The usefulness of thiolated chitosans as carrier matrices for controlled drug release was demonstrated with model drugs, such as clotrimazole and salmon calcitonin. The release of clotrimazole out of matrix tablets based on chitosan-thioglycolic acid conjugate or chitosan thiobutyl amidine (TBA) conjugate was quantified. Both tablets remained stable during the whole period of experiment (6hrs) and no

disintegration could be observed. However, only chitosan-TBA conjugate was able to guarantee a significant delay in drug release, compared to unmodified chitosan. The release profile of salmon calcitonin was observed as pseudo zero order over the first 8 hours. The tablets swelled during the experiment and release the active agent via a controlled diffusion process [5, 13, 14].

### **Formulations:**

#### **1) Matrix tablets**

Mucoadhesive matrix tablets are useful for intraoral, peroral, ocular and vaginal- local or systemic delivery. Due to the insitu cross linking properties of thiomers the cohesiveness and subsequently the stability of the swollen carrier matrix can be guaranteed [4]. The swelling behavior disintegration time and mucoadhesiveness of tablets compressed out of both thiolated and unmodified polyacrylic acid (PAA) were evaluated. Thiolated polymer tablets showed a 3-fold more prolonged disintegration time than unmodified PAA tablets [15]. Another study reported that chitosan-TBA-insulin tablets showed a controlled released of insulin over 8hrs.

#### **2) Micro- and nanoparticles [16]:**

Micro- and nanoparticles based on anionic or cationic mucoadhesive polymers disintegrate very rapidly, unless multivalent cationic or anionic compounds such as  $Ca^{2+}$  ion or sulfate ions are added, respectively leading to stabilization via an ionic cross-linker. However the mucoadhesive properties of these polymers are strongly reduced. On the contrary, due to immobilization of thiol groups on well-established polymers their mucoadhesive properties are further improved, although micro- and nanoparticles being based on thiolated polymer s do not disintegrate. Because of the formation of disulfide bonds within the polymeric network, the particles are stabilized.

#### **3) Ocular inserts [17]:**

Thiomers which can form covalent disulfide bridges with cysteine- rich subdomains of mucin have used to prepare ocular inserts. Inserts made of thiomers were not soluble and had good cohesive properties, due to the formation of inter- and /or intra chain disulphide bonds within the polymeric network after hydration. Hornhof et al formulated inserts consisting of PAA450-cysteine conjugate, a thiolated PAA [Poly (acrylic acid)], by direct compression and evaluated by fluorophotometry. The general irritation score indicated that the inserts were well accepted and tolerated.

#### **4) Transdermal patch [18]:**

A polymeric matrix using polycarbophil-cysteine (PCP-Cys) for transdermal progesterone application was developed and evaluated. The adhesive properties and release studies of PCP-Cys and PVP/HPMC and PVP/PVA were compared. From the results it was reported that the films based on PCP-Cys displayed very high cohesive properties due to the formation of inter chain disulphide bonds. Also the TWA (total work of adhesion) of the thiolated polymer on porcine skin was significantly the highest. In addition progesterone permeation was also the highest from PCP-Cys compared with PVP/HPMC and PVP/PVA within 24hrs.

#### **5) Coating for Liposomes [19]:**

A study to investigate the feasibility of preparing liposomes that are coated with the multifunctional polymer PAA-Cys was reported. Cationic multilamellar vesicles (MLV) as well

as cationic submicron-sized liposomes (ssLip) were prepared and coated with PAA-Cys. Size, zeta potential, amount of free thiol groups, aggregation behavior, drug-loading and drug release of these carriers were evaluated. No significant changes in size and zeta potential were observed. The results demonstrated that it is feasible to prepare PAA-Cys-coated liposomes and that they fulfill the basic requirements regarding stability, drug loading and drug-release for an intended use in oral drug delivery.

#### **6) Gels:**

Mucoadhesive gels are useful in case of intraoral, vaginal, nasal and ocular delivery. The advantage of use of thiomers in gel formulations has to be seen not only in their mucoadhesive but also in their insitu gelling properties. The potential of thiolated polycarbophil gels to provide a sustained release for Leucine-enkephalin (Leu-enkephalin) was reported. According to the study thiolated polycarbophil might be a promising excipient for nasal administration of Leucine-enkephalin [20]. Leitner et al developed a nasal gel formulation for systemic delivery of hGH. A comparative study with unmodified polycarbophil –cysteine in rats showed a significantly higher and prolonged nasal bioavailability of hGH which was incorporated in the thiomers gel formulation [4].

#### **7) Liquid formulations [4, 16]:**

Thiomers were found to be unstable in aqueous solutions but stable when stored in dry form. After the demonstration of Hornof that thiomers can be stabilized in aqueous solutions mucoadhesive liquid formulation comprising thiomers were prepared and tested *in vivo*. In particular in the ophthalmic field thiomers have already shown potential in form of liquid formulations. In case of the dry eye syndrome, liquid thiomers formulations might be beneficial. Because of their ability to interact with cysteine-rich subdomains of mucus glycol proteins on the ocular surface, eye drops containing a thiomers should be able to prolong the stability of the precorneal tear film for a comparable longer time period. A comparative study with established commercial product, eye drops containing thiolated polyacrylic acid had a positive effect on the tear film stability.

#### **Applications:**

##### **Controlled Drug Delivery**

A study was done to verify the potential of chitosan thio butyl-amidine (TBA) microsphere as carrier systems for controlled drug delivery. Microspheres were prepared using 0.5% of chitosan-TBA conjugate. The results attained from *in vitro* release studies with fluorescein isothiocyanate labeled dextran loaded chitosan TBA microspheres showed a controlled release rate for more than 3 hours while the control reached the maximum peak level of release already within an hour. According to these results chitosan TBA microspheres seem to be a promising tool in transmucosal drug delivery for poorly absorbed therapeutic agents [21].

In recent years thiomers have appeared as a promising new tool in oral drug delivery. Owing to the formation of inter and intra molecular disulfide bonds within the thiomers itself, matrix tablets and particulate delivery systems show strong cohesive properties, resulting in comparative higher stability, prolonged disintegration times and a more controlled drug release. The permeation of hydrophilic macromolecular drugs through the GI mucosa can be improved by the use of

thiomers. Some thiomers exhibit improved inhibitory properties towards GI peptidases. The efficacy of thiomers in oral drug delivery has been demonstrated by various *in vivo* studies. [22].

#### **Intravaginal Drug Delivery [23]**

For intra-vaginal 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. Being applied in liquid form, they become highly viscous gels in the vagina, which avoids an unintentional elimination and outflow of the semisolid delivery system. Due to the enzyme inhibitory effect thiomers can significantly improve the bioavailability of intra-vaginally administered drugs. Thiomers formulations can be intra-vaginally administered in the form of liquids, gels, tablets and capsules. Once applied, they remain on the vaginal mucosa even for weeks guaranteeing a controlled drug release over the intended time period.

#### **Nasal Drug Delivery [20]**

Thiolated polymers have been demonstrated to show a strong permeation enhancing effect for the uptake of drugs from the nasal mucosa. A study was carried out to evaluate the potential of thiolated polycarbophil for the nasal administration of Leu-enkephalin. The enzymatic degradation of Leu-enkephalin on bovine nasal mucosa was analyzed. The results showed that in presence of thiolated polycarbophil, degradation process is lowered. Diffusion studies demonstrated SR of Leu-enkephalin from thiolated polycarbophil gel. The permeation studies showed 82-fold improvement in the uptake of Leu-enkephalin from the nasal mucosa. Thus, thiolated polycarbophil might be a promising excipient for nasal administration of Leu-enkephalin.

#### **Protein and Peptide Drug Delivery [24]**

Till recent, injections remained the most common means for administering therapeutic proteins and peptide because of their poor oral bioavailability. The efficacy of thiomers in non invasive peptide delivery could be demonstrated by various *in vivo* studies. Tablets comprising thiomers and pegylated insulin, for instance, resulted in a pharmacological efficacy of 7% after oral application to diabetic mice. Furthermore, a pharmacological efficacy of 1.3% was achieved in rats by oral administration of calcitonin tablets comprising a thiomers. Human growth hormone in a thiomers-gel was applied nasally to rats and led to a bioavailability of 2.75%. In all these studies, formulations comprising the corresponding unmodified polymer had only a marginal or no effect. According to these results drug carrier systems based on thiomers seem to be a promising tool for non-invasive peptide drug delivery [2].

#### **Transdermal Drug Delivery [25]**

The use of PCP – Cys as polymeric matrix for transdermal application of progesterone was evaluated by Claudia Valenta *et al*. Films based on PCP- Cys displayed very high cohesive properties and the total work of adhesion of the thiolated polymer on porcine skin was found to be significantly highest. In addition progesterone permeation was also the highest from PCP Cys compared with PVP/ HPMC and PVP / PVA within 24 hrs. Thus authors concluded that PCP-Cys thiolated polymers might be a novel polymer matrix for transdermal progesterone delivery.

**Nucleic Acid Drug Delivery** [26]

Various studies identify thiolated chitosan as a promising new vector for gene delivery. Nanocomplexes of unmodified chitosan or thiolated chitosan with plasmid DNA encoding green fluorescent protein were characterized for their size, zeta potential, their ability to bind and protect plasmid DNA from degradation. The transfection efficiency of thiolated chitosan and sustained gene expression were evaluated. The results showed that thiolated chitosan condense pDNA to form nanocomplexes, which exhibit a significantly higher gene transfer potential and sustained gene expression upon cross linking indicating their great potential for gene therapy and tissue engineering.

**Ocular Drug Delivery** [27]

For the assembling of nanoparticulate ocular drug delivery system with mucoadhesive property, a thiolated nonionic surfactant, cysteine-PEG stearate was developed. Studies revealed that the encapsulated cyclosporine was found to remain on the ocular surface in the cul-de-sac for up to 6h, both precorneal retention time and concentration were dramatically increased compared with the nanostructural lipid carrier without thiomers modification.

**Buccal Drug Delivery** [28]

The benefit of thiolated polymers for the development of buccal drug delivery systems was investigated. L-cysteine was thereby covalently attached to polycarbophil mediated by a carbodiimide. Matrix tablets based on unmodified polymer and conjugated polymer were prepared and evaluated for their tensile strength, enzyme inhibitory property, disintegration time and mucoadhesive property. Results of the studies suggest that thiolated polymers represent a very useful tool for buccal delivery of drugs.

**CONCLUSION**

Thiolation of well-established polymers causes a dramatic change in the polymer's properties. Mucoadhesiveness, cohesiveness, insitu gelling properties etc are strongly improved. In view of drug delivery, the improved properties render these polymers a valuable tool which increases the drug bioavailability. Due to their high molecular mass thiomers are not absorbed from the GI mucosa. Hence systemic toxic side effects can be excluded. Also well established and safe polymers are selected as the backbone. These features make the thiomers technology highly interesting for non-invasive delivery route. The potential of thiolated polymers are already demonstrated by various *in vivo* studies. Thus thiomers seem to represent a promising candidate of polymeric excipients.

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