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Review Article

Thiolated chitosans: useful excipients for oral drug delivery

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Abstract

To improve the bioavailability of orally administered drugs, formulations based on polymers are of great interest for pharmaceutical technologists. Thiolated chitosans are multifunctional polymers that exhibit improved mucoadhesive, cohesive and permeation-enhancing as well as efflux-pump-inhibitory properties. They can be synthesized by derivatization of the primary amino groups of chitosan with coupling reagents bearing thiol functions. Various data gained in-vitro as well as in-vivo studies clearly demonstrate the potential of thiolated chitosans for oral drug delivery. Within the current review, the synthesis and characterization of thiolated chitosans so far developed is summarized. Features of thiolated chitosans important for oral drug delivery are discussed as well. Moreover, different formulation approaches, such as matrix tablets and micro-/nanoparticles, as well as the applicability of thiolated chitosans for the oral delivery of various substance classes including peptides and efflux pump substrates, are highlighted.

Introduction

Due to obvious advantages, such as painless administration and good patient compliance, oral drug delivery is highly demanded by patients and the pharmaceutical industry. Unfortunately, by no means all drugs can be administered via this route. Especially, hydrophilic macromolecules such as therapeutic peptides and proteins, nucleotides such as pDNA or siRNA, as well as efflux pump substrates, are in general substance classes with negligible oral bioavailability. This is due to the barriers encountered with the oral route: gastrointestinal enzymes can lead to a rapid degradation or metabolism of orally administered drugs (Woodley 1994; Bernkop-Schnürch 1998); efflux pumps such as P-glycoprotein can actively transport drugs back into the intestinal lumen (Varma et al 2006); the physical permeation barrier caused by the mucus as well as the gastrointestinal epithelium itself must be overcome (Bernkop-Schnürch & Fragner 1996); and also the physico-chemical properties of the drug, such as low solubility, can be responsible for low drug plasma levels after oral administration (Swarbrick & Boylan 2002).

To overcome these barriers, researchers either modify the drug itself, or the original drug is administered in an oral drug delivery system. These delivery systems can be based on specific auxiliary agents such as enzyme inhibitors, permeation enhancers or efflux pump inhibitors, on particulate systems such as micro- and nanoparticles or liposomes or on polymers. Some polymers (so-called multifunctional polymers) combine several properties beneficial for oral drug delivery, including mucoadhesive properties and permeation-enhancing properties.

One of the most widely used multifunctional polymers is chitosan. This cationic polysaccharide is produced by deacetylation of the naturally occurring chitin, which can be found in high concentrations in the shells of crustaceans. Chitosan is soluble at acidic pH, whereas it is insoluble at alkaline and neutral pH. Its mucoadhesive properties are mediated by ionic interactions of the positively charged amino groups and negatively charged substructures of the gastrointestinal mucus, mainly sialic acid. Permeation by paracellular transported drugs can be improved by the opening of tight junctions. Moreover, nanoparticles consisting of chitosan and nucleotides can be produced easily due to ionic interactions between

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the positively charged polymer and the negatively charged nucleotide. Due to these beneficial features for oral drug delivery, several groups worldwide work on the modification of chitosan to further improve its properties. Besides derivatives such as trimethylated chitosan (Thanou et al 2000), mono-*N*-carboxymethyl chitosan (Thanou et al 2001), *N*-sulfo-chitosan (Baumann & Faust 2001) and chitosan–EDTA conjugates (Bernkop-Schnürch et al 1997), thiolated chitosans have been found to be highly promising for oral drug delivery. Up to date, five different thiolated chitosans, including chitosan–thioglycolic acid (chitosan-TGA) conjugates (Kast & Bernkop-Schnürch 2001; Hornof et al 2003), chitosan–cysteine (chitosan-Cys) conjugates (Bernkop-Schnürch et al 1999), chitosan–glutathione conjugate (chitosan-GSH) (Kafedjiiski et al 2005a), chitosan–thioethylamidine conjugate (chitosan-TEA) (Kafedjiiski et al 2005b, 2006) and chitosan–4-thio-butyl-amidine conjugate (chitosan-TBA) (Bernkop-Schnürch et al 2003), have been synthesized and evaluated. The structures of these conjugates are provided in Figure 1. It could be demonstrated that this lated chitosans exhibit strongly improved mucoadhesive and permeation-enhancing properties. Furthermore, recent studies showed that thiolated chitosans are capable of inhibiting efflux pumps. Also, their potential for non-viral oral gene delivery could be demonstrated. Based on their high cohesive properties, a controlled drug release can be achieved.

It is the aim of this review to provide information regarding the application of the thiolated chitosans so far synthesized as oral delivery systems for therapeutic peptides and proteins, efflux pump substrates and nucleotides. Results of in-vitro as well as in-vivo studies will be discussed.

Synthesis and types of thiolated chitosans

Generally, the primary amino group of the glucosamine subunits of chitosan is the main target for the covalent attachment of thiol groups. As shown in Figure 1, sulfhydryl-bearing agents can be immobilized to this primary amino group via the formation of amidine and amide bonds. Amidine bonds are formed by thiobutylamidine and thioethylamidine ligands, whereas amide bonds are formed with cysteine, *N*-acetylcysteine, glutathione and thioglycolic acid mediated by water-soluble carbodiimides. The formation of disulfide bonds by air oxidation during the synthesis process can be avoided by performing the process at pH $\leq$ 5. At this pH, the concentration of thiolate-anions, representing the reactive form for oxidation of thiol groups, is negligible, and the formation of disulfide bonds can be quenched. Alternatively, the coupling reaction can be performed under inert conditions or with S-protected ligands, such as thioesters, that can be cleaved after the coupling reaction (e.g. with hydroxylamine).

The amount of immobilized thiol groups in reduced and oxidized form can be determined via Ellman's reagent (Hornof et al 2003) with and without previous quantitative reduction of disulfide bonds with borohydride (Habeeb 1973). In addition, iodometric titration can be utilized to determine the amount of immobilized thiol groups.

Properties of thiolated chitosans

Mucoadhesion

Among the mucoadhesive polymers currently used in oral drug delivery, thiomers, such as thiolated chitosans, display the most pronounced mucoadhesiveness. Whereas the mucoadhesive properties of polymers such as unmodified chitosan or poly(acrylic acid) are mediated by ionic interactions or physical effects such as interpenetration, the mucoadhesive properties of thiolated chitosans are based on covalent bonds between the polymer and the mucus. The free thiol groups of thiolated chitosans are capable of forming disulfide bonds with cysteine-rich subdomains of the mucus. An improvement in the mucoadhesive properties of thiolated chitosan in comparison to unmodified chitosan could be demonstrated in-vitro with both tensile studies and the rotating cylinder method. In tensile studies, it was demonstrated that there is a positive correlation between the amount of free immobilized thiol groups and the mucoadhesive properties of the polymer (Kast & Bernkop-Schnürch 2001; Roldo et al 2003). Moreover, a prolonged retention time of tablets based on a thiolated chitosan matrix in comparison to tablets consisting of unmodified chitosan was observed when evaluating the matrix tablets with the rotating cylinder method (Kafedjiiski et al 2005a, 2006).

Chitosan-TGA was the first thiomer that was developed using chitosan as the polymeric backbone. In comparison to unmodified chitosan, a 6- to 10-fold increase in mucoadhesion using tensile studies occurred. Mucoadhesion of chitosan-TEA was improved 5.1-fold using tensile studies and around 13-fold when using the rotating cylinder method in comparison to unmodified chitosan. Using the rotating cylinder method, chitosan-GSH tablets stuck to the mucosa for around 166 h, which means a 55-fold improvement in comparison to unmodified chitosan. Depending on the molecular mass of the utilized chitosan-TBA conjugate, the mucoadhesiveness was improved up to 100-fold. Data summarizing the improved mucoadhesion of thiolated chitosans, as well as the according literature, is provided in Table 1. Regarding the molecular mass of the chitosan backbone, it could be demonstrated that best results were achieved when using medium-molecular-mass chitosan. The pronounced mucoadhesive properties of chitosan-TBA and chitosan-TEA, also in comparison to other mucoadhesive thiomers, might also be partly be mediated by additional ionic interaction between the amidine substructure of these thiolated chitosans and the negatively charged substructures of the mucus (Roldo et al 2003).

Permeation enhancement

One reason why chitosan is widely used in oral drug delivery is that it is capable of improving the permeation of hydrophilic drugs such as peptides, proteins and oligonucleotides (Illum et al 1994). During permeation studies performed with Caco-2 monolayers and in the presence of chitosan, a reversible decrease in trans-epithelial electric resistance (TEER) was observed, which can most likely be explained by the reversible opening of tight junctions. It is believed that ionic interactions between chitosan and the cell membrane lead to structural reorganization of tight-junction-associated proteins (Artursson et al 1994; Borchard et al 1996; Dodane et al 1999). The permeation-enhancing effect of chitosan in the presence of the mucus

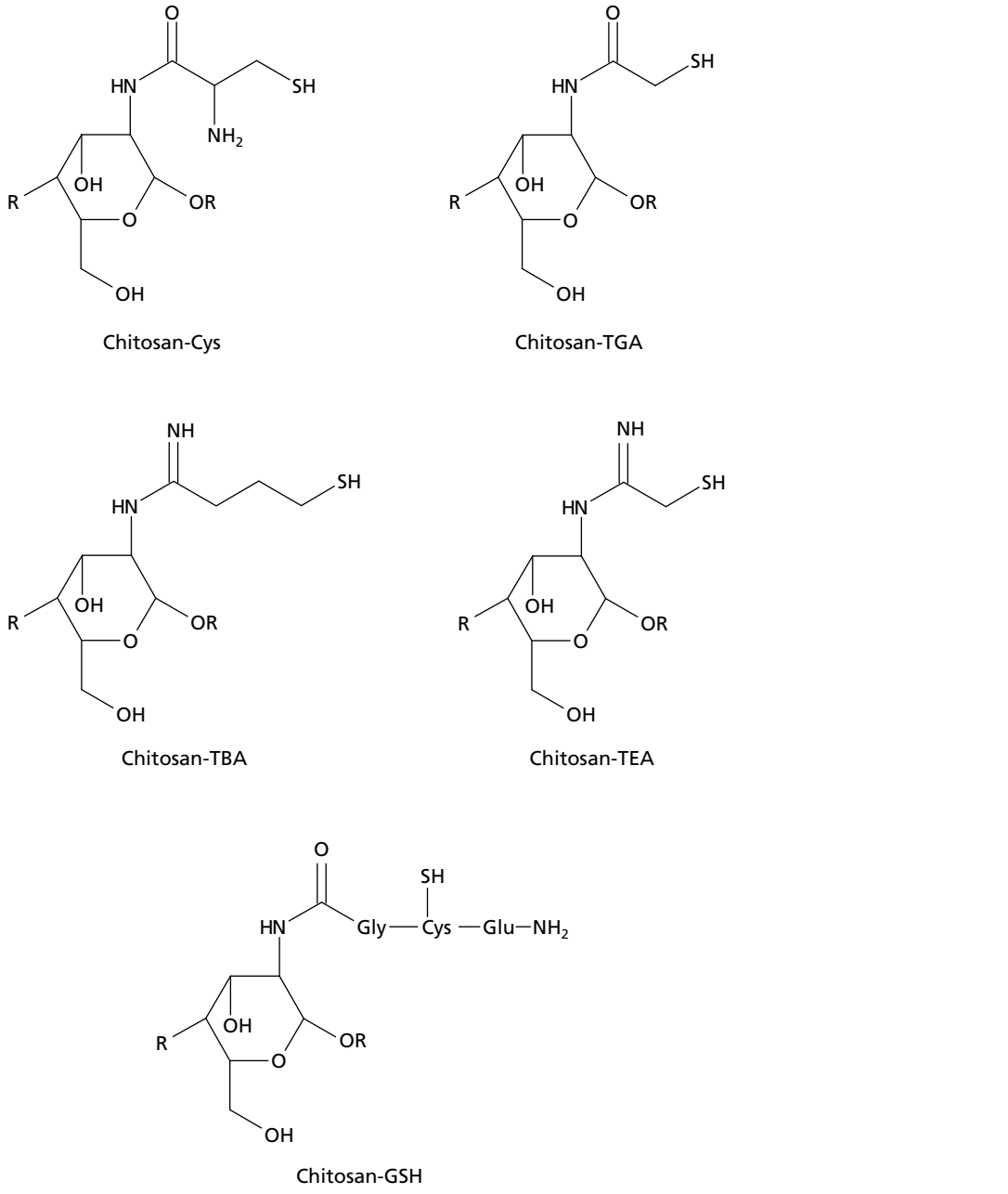

Figure 1 Presumptive chemical substructures of thiolated chitosans.

layer, however, is lower than the effect that can be observed when performing the experiments with monolayers. This is due to the limited diffusion of the polymer into the mucus or charge interactions of chitosan with mucins (Schipper et al 1999). Although these observations might lead to the conclusion that chitosan is not a potent permeation enhancer in-vivo, it was demonstrated in rats that the oral bioavailability of the peptide drug buserelin increased after co-administration of chitosan-HCl (Luessen et al 1996).

The permeation enhancing-effect of chitosan can be markedly improved by the immobilization of thiol groups. Data from various permeation studies are available, that clearly demonstrate the potential of thiolated chitosan. By way of example, in permeation studies performed with Ussing type permeation chambers and freshly excised rat intestinal mucosa, it could be shown that the permeation of a cystine-knot microprotein (CKM) increased about 3-fold when co-administering a combination of chitosan-TBA and unbound reduced glutathione (GSH) (Werle et al 2007). The time-dependent CKM permeation in the presence of this chitosan-TBA/GSH delivery system in comparison to the permeation of CKM in buffer only

Table 1 The mucoadhesive properties of chitosan-TGA, chitosan-TBA, chitosan-TEA and chitosan-GSH in comparison with unmodified chitosan evaluated by the rotating cylinder method

Polymer	Degree of modification (μM g^{-1})	Improvement ratio	Reference
Chitosan-TGA	10	0.9	Kast & Bernkop-Schnürch 2001
	27	5	
Chitosan-TBA	60	123	Bernkop-Schnürch et al 2003
	95	>140	
Chitosan-TEA	225	13	Kafedjiiski et al 2006
Chitosan-GSH	266	55	Kafedjiiski et al 2005a

Improvement ratio = adhesion time of thiolated chitosan divided by adhesion time of unmodified chitosan.

is shown in Figure 2. Also, chitosan-TEA/GSH improved rhodamine-123 permeation through rat intestinal mucosa 3-fold and chitosan-GSH/GSH even improved rhodamine permeation 4.9-fold. Thiolated chitosan concentrations in those in-vitro studies are usually 0.5%. The permeation-enhancing effect of different thiolated chitosans is provided in Table 2.

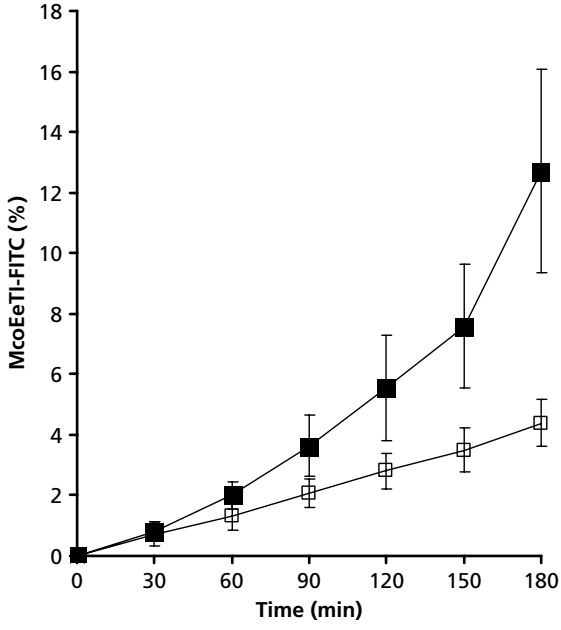

Figure 2 Permeation-enhancing effect of the peptide McoEeTI through rat intestine in presence of chitosan-TBA/GSH (■, McoEeTI-FITC + 0.5% chitosan-TBA+2.5% GSH; □, McoEeTI-FITC in buffer) Each point represents the mean ± s.d. of at least 3 experiments (figure adapted from Werle et al (2007)).

Analogous to unmodified chitosan, the underlying effect of thiolated chitosans is believed to be based on an opening of the tight junctions. More precisely, the mechanism has been ascribed to be based on the inhibition of protein tyrosine phosphatase, an enzyme that is involved in the opening and closing process of the tight junctions. Protein tyrosine phosphatase is responsible for the dephosphorylation of tyrosine subunits of occludin, representing an essential transmembrane protein of the tight junctions. Dephosphorylation of the tyrosine subunits of occludin leads to the closing of the tight junctions, whereas a phosphorylation of these subunits leads to an opening of the tight junctions. Therefore, the inhibition of protein tyrosine phosphatase leads to phosphorylation and consequently to an opening of the tight junctions (Clausen et al 2002). Thiolated chitosans are able to shift the balanced concentration of oxidized and reduced GSH on the mucosal membrane to the side of reduced GSH, which is capable of inhibiting protein tyrosine phosphatase (Barrett et al 1999). The thiolated chitosan is oxidized and oxidized GSH is consequently reduced. This process leads to an increase in the concentration of reduced GSH on the membrane, which inhibits protein tyrosine phosphatase and opens the tight junctions. Furthermore, delivery systems based on a combination of thiolated chitosan and reduced GSH display even more pronounced permeation-enhancing effects.

Efflux pump inhibition

Besides their potential as drug delivery systems for hydrophilic macromolecules, thiolated chitosans have also been evaluated regarding their efficacy to improve the oral delivery of efflux pump substrates. The oral bioavailability of drugs, including paclitaxel, ciclosporin and doxorubicin, is strongly limited by intestinal located efflux pumps such as P-glycoprotein. Excipients that can inhibit efflux pumps are therefore capable of improving drug uptake of such substrates (Werle 2007). Recently, it has been demonstrated that thiomers can inhibit efflux pumps (Werle & Hoffer 2006). Bi-directional transport studies of the P-glycoprotein (P-gp) substrate rhodamine-123 using freshly excised guinea-pig ileum have been performed with Ussing-chambers. In buffer only, the apical-to-basolateral (A-B) drug transport was lower than the basolateral-to-apical (B-A) drug transport, resulting in an efflux ratio (B-A / A-B) of 2.8. This ratio decreased when different concentrations of chitosan-TBA or GSH were co-administered. Using a combination of 0.5% chitosan-TBA and 0.5% GSH, even an efflux ratio < 1 was achieved, indicating total efflux pump inhibition. In Figure 3, the transport of the P-gp substrate rhodamine-123 from A-B and B-A in buffer only and the transport of rhodamine-123 from A-B and B-A in the presence of 0.5% chitosan-TBA is shown. Moreover, the A-B transport of the efflux pump substrate saquinavir through Caco-2 monolayers increased in the presence of chitosan-TBA/GSH. No data regarding the efflux pump inhibitory activity of unmodified chitosan could be found. Therefore, it is most likely that the efflux pump inhibitory activity of thiomers is mediated by the introduced thiol groups. The exact mechanism is currently not known, although interactions with ATP binding sites can be excluded, as thiolated chitosans do not permeate the cell membrane. Possible explanations are alterations of the cell membrane or

Table 2 Permeation-enhancing properties of thiolated chitosans in comparison with the unmodified polymers tested on freshly excised intestinal mucosa

Permeation enhancer	Test compound	Enhancement ratio	Reference
Chitosan-Cys	Bac-FITC	—	Bernkop-Schnürch et al 1999
Chitosan-TBA	Rhodamine-123	2.0	Bernkop-Schnürch et al 2004
Chitosan-TBA/GSH	Rhodamine-123	3.6	Bernkop-Schnürch et al 2004
Chitosan-TEA/GSH	Rhodamine-123	3.1	Kafedjiiski et al 2006
Chitosan-GSH	Rhodamine-123	3.1	Kafedjiiski et al 2005a
Chitosan-GSH/GSH	Rhodamine-123	4.9	Kafedjiiski et al 2005a

Enhancement ratio is the apparent permeation coefficient (P_{app}) of the test compound in the presence of the thiolated chitosan divided by the P_{app} in the presence of unmodified chitosan.

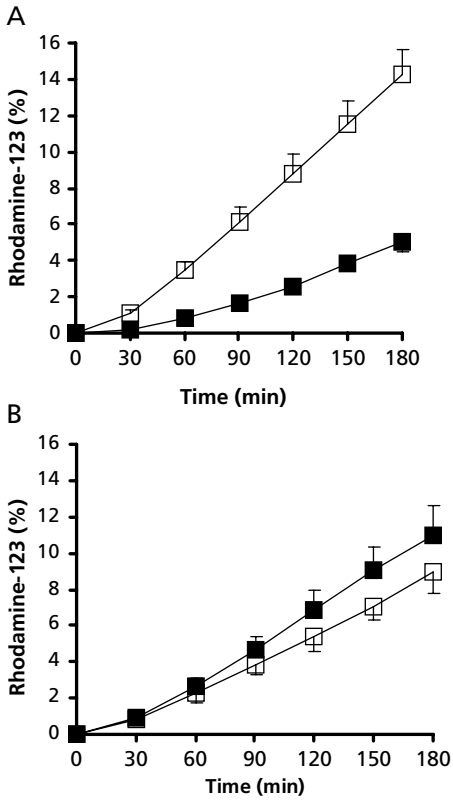

Figure 3 Transepithelial transport of rhodamine-123 in the absorptive (■) and secretory direction (□) in the absence (A) or presence (B) of chitosan-TBA at a concentration of 0.5% (m/v) (figure adapted from Werle & Hoffer (2006)).

the formation of disulfide bonds between free thiol groups of the thiolated chitosan and cysteine subunits located in the transporter channel formed by the transmembrane domains. Especially, interactions between thiolated chitosan and the cysteine of two channel-forming transmembrane domains, namely 2 and 11, are likely (Bernkop-Schnürch & Grabovac 2006). So far, chitosan-TBA is the only thiolated chitosan that has been evaluated regarding its potential for efflux pump inhibition (Werle & Hoffer 2006).

Controlled release

Mucoadhesive dosage forms are only effective if a controlled drug release over a certain time period can be guaranteed. Furthermore, the combination of mucoadhesive and cohesive features is a pre-requisite for effective mucoadhesive oral drug delivery systems.

The free thiol groups of thiolated chitosans can, besides interacting with the mucus, form inter- and intramolecular disulfide bonds, leading to a high cohesiveness of the polymeric network. This theory was confirmed by the decrease in free thiol groups within thiomers during an oxidation experiment, resulting in an increased viscosity (Bernkop-Schnürch et al 2003). Such a cross-linking of the polymeric chains results in a highly stable, three-dimensional matrix that allows a controlled drug release. The efficacy of thiolated chitosans as carrier matrices for controlled drug release was demonstrated by means of model drugs, like clotrimazole (Kast et al 2002; Bernkop-Schnürch et al 2003) or salmon calcitonin (Guggi et al 2003a, b).

Calcitonin is used in the treatment of osteoporosis and is, besides insulin, one of the best investigated peptide drugs for oral administration. The release profile of salmon calcitonin out of matrix tablets based on the chitosan-TBA conjugate was investigated. Over the first 8 h, a pseudo zero-order release profile of salmon calcitonin was observed in artificial intestinal fluid (Figure 4). During the experiment a continuous swelling of the tablets was observed; the tablets maintained a good cohesiveness and released the peptide via a controlled diffusion process (Torres-Lugo & Peppas 2000). Furthermore, chitosan-TGA and chitosan-TBA have shown excellent in-situ gelling properties, with a clear correlation between the total amount of polymer-linked thiol groups and the increase in viscosity of the formed gel (Hornof et al 2003).

Formulations

Matrix tablets

Thiolated chitosans can be easily compressed to form matrix tablets. Due to the in-situ cross-linking properties of thiolated chitosans, the cohesiveness, as well as the stability, of the swollen carrier matrix can be guaranteed (Bernkop-Schnürch et al 2003). To avoid the low pH or degradation mediated by pepsin in the stomach, matrix tablets can be enteric coated. On the other hand, if an adhesion is already achieved in

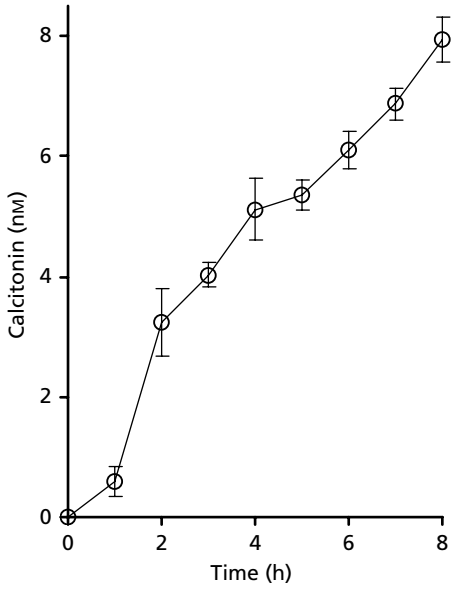

Figure 4 Release profile of salmon calcitonin from 2-mg tablets having chitosan-TBA conjugate as substantial excipient. Each point represents the mean ± s.d. of 3 experiments (Figure adapted from Guggi et al (2003a)).

the stomach, coating with a triglyceride seems to be sufficient to avoid an unintended adhesion in the oral cavity or oesophagus (Guggi et al 2003b). As already described, matrix tablets based on thiolated chitosans offer the advantage that controlled drug release can be easily achieved out of this type of mucoadhesive dosage form, which has already be demonstrated for numerous drugs (Guggi et al 2003b; Bernkop-Schnürch et al 2005). The production of the tablets themselves is quite easy—simply homogenizing the thiolated chitosan with the drug of choice and compressing tablets out of it results in many cases in delivery systems that can guarantee even a zero-order release profile for several hours (Guggi et al 2003a). The release rate of the drug is thereby mainly controlled by a hydration and diffusion process.

Micro- and nanoparticles

Micro- and nanoparticulate delivery systems often exhibit improved features for oral drug delivery in comparison to matrix tablets. In the case of micro- and nanoparticles based on thiolated chitosans, this can be attributed to the improved mucoadhesive features of such particulate systems. Moreover, also the fact that a drug that is released from a mucoadhesive particulate system is less affected by luminally secreted enzymes in comparison to a drug that is released from a matrix tablet might contribute to a better performance in-vivo.

By diffusing into the mucus gel layer by virtue of their relatively small size, micro- and nanoparticles show a prolonged gastrointestinal residence time even without any mucoadhesive properties (Ponchel 1997). Particulate delivery systems show, therefore, a more prolonged gastrointestinal transit time compared with single-unit dosage forms (Coupe et al 1991). To further improve the residence time of drug delivery systems on mucosal membranes, micro- and nanoparticles were consequently combined with mucoadhesive polymers. Micro- and nanoparticles based on unmodified chitosans, however, disintegrate very rapidly, unless multivalent anions, such as tripolyphosphate or sulfate, are added (Ko et al 2003). Unfortunately, such ionic cross-linkers strongly reduce the mucoadhesive properties of chitosan. In contrast, due to the immobilization of thiol groups on well-established polymers, their mucoadhesive properties are even further improved, although micro- and nanoparticles based on thiolated polymers do not disintegrate. The formation of disulfide bonds within the polymeric network strongly improves the stability of these particles (Bernkop-Schnürch et al 2006a). In general, the preparation of thiolated chitosan micro- and nanoparticles is based on the following steps. In the first step thiolated chitosan is ionically gelated with tripolyphosphate or sulfate in aqueous solution. In the second step thiol groups in and on the particles are partially oxidized, forming stabilizing inter- and intramolecular disulfide bonds. As the degree of oxidation can be well controlled during the preparation process, the content of thiol and disulfide groups can be adjusted. In the third step the polyanions are removed. Utilizing this preparation technique, as illustrated in Figure 5, stable particles of a mean size in the range from 100 nm up to 10 μm can be generated.

Particles prepared in this way show strongly improved mucoadhesive properties. The more thiol groups are oxidised within the particles, however, the lower is the improvement in mucoadhesive properties. Nevertheless, even when 91% of all thiol groups on the nanoparticles are oxidized, their mucoadhesive properties are still 2-fold higher than those of unmodified chitosan nanoparticles (Bernkop-Schnürch et al 2006b).

In-vivo studies

Several in-vivo studies that demonstrate the efficacy of thiolated chitosans in improving the oral bioavailability of therapeutic peptides and proteins have been published. Besides hydrophilic macromolecules, it has been demonstrated recently that also efflux pump substrates represent a substance class for which the oral bioavailability can be improved when using thiolated-chitosan-based drug delivery systems.

Enteric-coated matrix tablets based on chitosan-TBA containing the drug salmon calcitonin, which is used in the treatment of osteoporosis, were developed. As well as the thiolated chitosan, the tablets also contained two different chitosan–enzyme inhibitor conjugates, namely chitosan-Bowman Birk inhibitor conjugate and chitosan-elastatinal, so as to avoid enzymatic degradation during gastrointestinal passage (Guggi & Bernkop-Schnürch 2003). After oral administration of the tablets to rats, the time-dependent calcium plasma level was monitored. The control group received an oral solution containing salmon calcitonin. No decrease in the calcium level could be observed in this group. Furthermore, also no decrease in plasma calcium occurred in the group that received salmon calcitonin in tablets based on chitosan only, although chitosan displays mucoadhesive as well as permeation-enhancing properties. After oral administration of chitosan-TBA tablets containing salmon calcitonin,

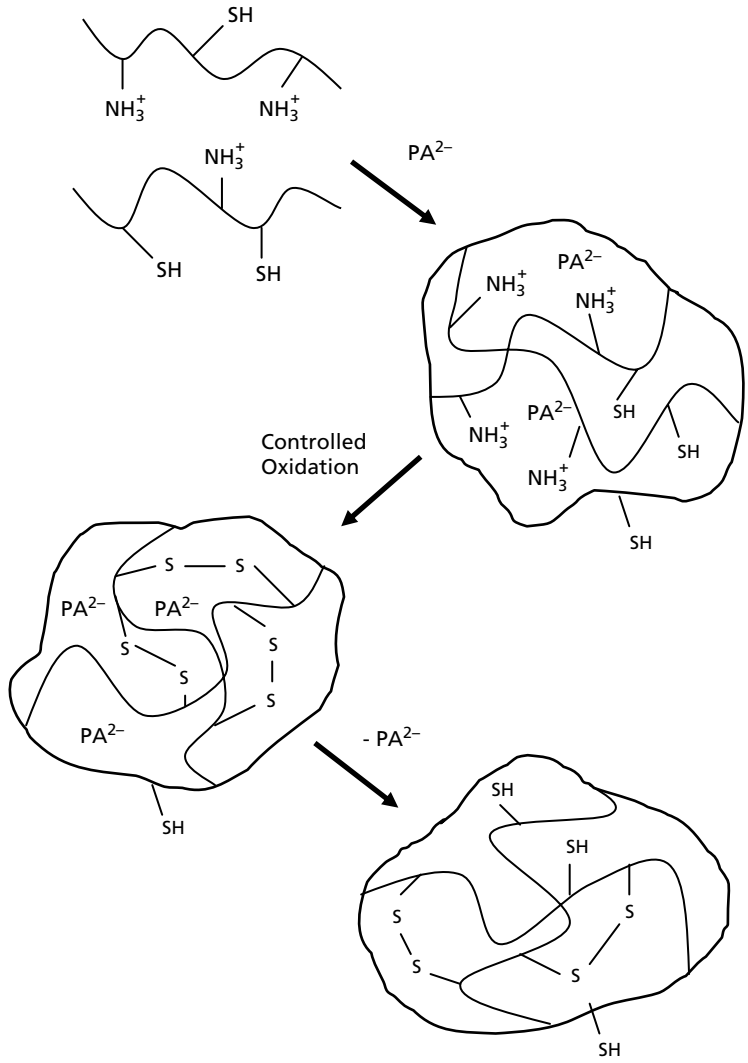

Figure 5 Illustration of thiolated chitosan micro- and nanoparticle preparation by using polyanions (PA^{2-}).

the plasma calcium level decreased for several hours for more than 5% of the initial value (Guggi et al 2003a).

In another study, a stomach-targeted delivery system for salmon calcitonin was developed. To minimize calcitonin degradation by pepsin, the tablets contained chitosan–pepstatin conjugate. The thiolated chitosan used was chitosan-TBA. A pharmacological efficacy of 1.35% was achieved, calculated on the basis of the area under the reduction in plasma calcium levels of the oral matrix tablets versus intravenous injection. The results of this in-vivo study are provided in Figure 6 (Guggi et al 2003b).

The efficacy of chitosan-TBA/GSH for oral drug delivery has furthermore been studied with the peptide antide. The drug was administered intravenously, subcutaneously and orally in solution as well as in chitosan-TBA/GSH tablets. Whereas antide could not be detected in plasma samples after oral administration of the solution, the absolute and relative bioavailability of antide after oral administration of the chitosan-TBA / GSH tablets was determined to be 1.1% and 3.2%, respectively (Bernkop-Schnürch et al 2005)

The use of thiolated chitosans for the oral delivery of efflux pump substrates is a comparatively young research field. The first in-vivo study demonstrating the efficacy of thiolated chitosan for the oral delivery of efflux pump substrates was performed with the P-gp substrate rhodamine-123. In Figure 7, the effect of chitosan-TBA / GSH on the oral uptake of rhodamine-123 in comparison with rhodamine-123 uptake administered in solution is provided. Moreover, Föger et al (2006a, b) showed that oral administration of tablets containing a combination of chitosan-TBA and GSH led to significantly improved rhodamine-123 plasma levels in rats in comparison to tablets based on either poloxamer or Myrj, which are two polymers that are known to inhibit P-gp. Another study with chitosan-TBA was performed with the HIV drug saquinavir, which is a substrate of MRP 2 and P-glycoprotein. An improved uptake of saquinavir in

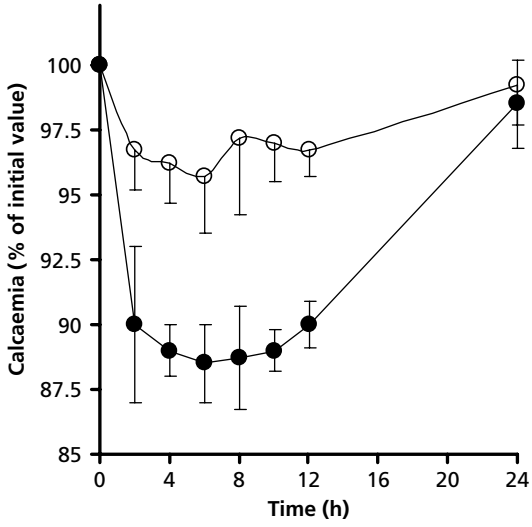

Figure 6 Effect of chitosan / chitosan-pepstatin (○) and chitosan-TBA / chitosan-pepstatin (●) on blood calcium level in rats after oral administration (Figure adapted from Guggi et al (2003b)). Each value represents the mean ± s.d. of at least three experiments.

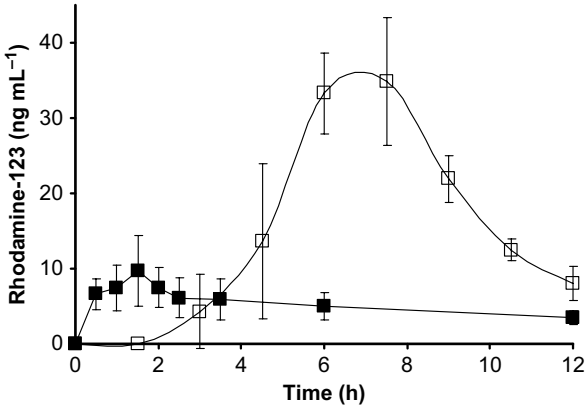

Figure 7 Plasma concentration of rhodamine-123 after oral administration of 1.5 mg rhodamine-123 in solution (■) and in chitosan-TBA / GSH tablets (□). Each value represents the mean ± s.d. of 5 experiments (Figure adapted from Föger et al (2006a)). Each value represents the mean ± s.d. of at least three experiments.

presence of a thiomer/GSH system was demonstrated (Föger et al 2006c).

Conclusion

The immobilization of thiol groups on chitosan leads to strongly improved features that are of great importance for oral drug delivery. The mucoadhesive properties, as well as the permeation-enhancing properties, of chitosan can be increased by such modifications. Moreover, thiolated chitosans display improved cohesiveness, allowing a controlled drug release. The recently demonstrated capability of thiolated chitosans to inhibit efflux pumps offers new opportunities for the applicability of this class of polymers. Besides the use of thiolated chitosans for the oral delivery of hydrophilic macromolecules, including therapeutic peptides, proteins or nucleotides, thiolated chitosans have been evaluated to be efficient for the delivery of efflux pump substrates. Especially in combination with novel technologies, such as nanotechnology, thiolated chitosans are believed to represent an important tool for oral drug delivery.

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