THIOMERS; A BLESSING TO EVOLUTING ERA OF PHARMACEUTICALS

Muhammad Zaman*,1,2, Muhammad Hanif1, Sundas Qureshi2,

1 Department of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan
2 Faculty of Pharmacy, The University of Lahore

Corresponding Author

Muhammad Zaman
Department of Pharmacy
Bahauddin Zakariya University, Multan, Pakistan
Email Address: m.zaman2157@gmail.com
Contact: 0092-3006095928
Abstract

Thiomers are the polymers modified for the mucoadhesive properties and other additive properties by incorporating thiol moieties in the backbone of the unmodified polymeric chain by exchange reactions or simple oxidation reactions. Drug that are less soluble and permeable can be complexed with thiomers for their increased absorption through the mucosal membranes by increase in contact time and prolonged stay in body due to mucoadhesion. Immobilization of thiol group therefore increases the mucoadhesive properties of the modified polymer by 2-140 folds. The prepared thiomers are characterized and made stable by different techniques. Thiomers also give the controlled delivery of the active in the body. Different polymers that are modified by thiolation are chitosan, polyacrylic acid, sodium alginate, sodium carboxy methyl cellulose, guar gum etc. Thiomeric formulations are a challenge to deliver drugs with low therapeutic compatibility. Micro- and nano- preparations containing thiomers can be prepared by different techniques such as covalent crosslinking, insitu gelation, radical emulsion polymerization, emulsification etc. Nowadays thiomers have wide range of applications as a promising pharmaceutical excipient in the evaluating era of pharmaceutical technology.

Keywords: Thiomers, Thiolation, Mucoadhession
Introduction

Bioadhesion is the phenomenon by which any molecule adheres to the biological membrane but when the adherence to the mucus is specified it is referred to as mucoadhesion[1]. Mucoadhesion is introduced in the pharmaceutical field for more than 40 years and it is of main importance in oral delivery systems, as drugs taken from oral route have various bioavailability issues[2, 3]. Adhesion to the membranes is of importance as it prolongs the stay of the drug in the body subsequently increasing bioavailability of the drug which in turn improves patient compliance[4]. The natural or synthetic macromolecules are present that adhere to the mucus layer by interacting with the glycoproteins in the mucus, not by covalent bonding, but by weak ionic interactions such as, hydrogen bonding and Vander Waal’s forces[1, 5]. Nowadays, efforts are being made to increase the mucoadhesive properties of the polymer such as improved resistance to enzymes, increased cohesive force and facilitated paracellular diffusion of the drug, increased bioavailability and increased patient compliance[2, 6]. For this purpose, the new generation of mucoadhesive polymers developed by integrating sulfhydryl groups on the backbone of the polymer resulted in thiolated polymers, also called as thiomers[6, 7]. This structural modification in the polymer has led to the improvement in the mucoadhesive properties of the polymers by 2- to 140- folds[8]. Polymers modified are

- Alginate
- Chitosan [2]
- Polycarbophil[9]
- Polyacrylic acid [0]
- Xyloglucan [1]
- Carboxy methyl cellulose[12]
- polyaspartamide[13, 14]
- hydroxyethyl cellulose[15]

Types of Thiomers

Followings are the types of thiomers

- Cationic thiomers
- Anionic thiomers
Table 1: Examples of cationic and anionic polymers

<table>
<thead>
<tr>
<th>Cationic thiomers</th>
<th>Anionic thiomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyethyl cellulose</td>
<td>Poly acrylic acid cystamine conjugate</td>
</tr>
<tr>
<td></td>
<td>Sodium carboxy methyl starch (CMS)</td>
</tr>
<tr>
<td></td>
<td>Carboxy methyl guar gum (CMG)</td>
</tr>
<tr>
<td></td>
<td>Carboxymethyl cellulose</td>
</tr>
<tr>
<td></td>
<td>Sodium alginate</td>
</tr>
</tbody>
</table>

Chitosan

Cationic thiomer

Basically these are the thiomers based on chitosan, prepared by immobilizing thiol group on 2-amino position of the glucosamine, present in the polymer chain. Examples include chitosan-cysteine, chitosan-thioglycolic acid, chitosan-thiobutylamidine etc (table 1) [2].

Chitosan

Chitosan, a natural mucoadhesive polysaccharide polymer, obtained from deacetylation of chitin present in the crustacean shell, is chemically named as \( \text{poly \{(1, 4)-2-amino-2-deoxy-d-glucopyranose\}} \). It consists of two subunits N-acetylglucosamine and glucosamine[16]. Chitosan has the mucoadhesive and permeation enhancing properties due to interaction of the amino group with the anionic structures in the mucus or epithelial layer due to its polycationic nature[17]. The primary amino group present in glucosamine is easily protonated in acidic media which increases its solubility. While it remains stable in basic and neutral media[2, 18].

Modified generation of chitosan is prepared with more pronounced mucoadhesive properties by incorporating thiol group on the backbone of the polymer that is creating the thiolated chitosan[19]. Thiolated chitosan are with improved mucoadhesive properties, enhanced permeation and in situ gelling properties such as chitosan thio butyl amidine conjugate, chitosan cysteine conjugate, chitosan thioglycolic acid conjugate etc.[2, 20].

Increased mucoadhesive property of chitosan

Thiolated chitosan is the modified polymer having ability to bind with the mucin through covalent bonding rather than weak ionic interactions such as hydrogen bonding or vanderwaal’s forces as simple chitosan. Sulphur present in the thiolated chitosan make disulfide bonding with the cysteine rich domain of the mucin thus increasing time to stay in body which in turn
increases bioavailability and also may help to reduce dosing frequency which ultimately increase patient compliance[2].

**Mucin**

Mucin is a glycoprotein consisting of protein core with branched oligosaccharides over 63% of its length, makes 5% of total mucus. It accounts for gel like properties of the mucus. Cysteine present in the mucin glycoprotein account for 1.5% of the amino acid in the small intestine .i.e. about 9 µmol SH/g of mucus[2].

**Preparation of thiolated chitosan**

Thiolated chitosan is prepared by introducing the sulphydryl bearing moiety on the 2-amino position of the glucosamine subunit. This is done by reacting carboxylic group of the moiety such as cysteine or thioglycolic acid with the amino group in the polymer back bone leading to formation of the amide bond or amidine bond, in the presence of 1-ethyldiaminopropyl carbodimides (EDAC) or thiobutyric acid, respectively, as coupling agent. Thiol group may undergo oxidation so synthesis must be done under inert conditions or at pH <5, as at this pH the concentration of the thiol anions is low so disulfide formation seldom occurs[2, 4, 21].

The schemes of reactions involved in the formation of thiolated chitosan are shown in the figure below. It shows two schemes indicating one step process and two steps process. Single step processing of chitosan to achieve thiolated chitosan shows reaction medium consisting of water. The thiolation takes place in the presence of carbodimide (EDAC) and NHS (N-hydroxysuccinimide). While the second process involving the two steps; first step involves DMF (N,N-dimethylformamide) as a reaction medium to avoid hydrolysis of the ester formed thereby in the reaction. This scheme is shown in figure 1[18].
Studies have shown that immobilization of 25-250 µmol thiol groups per gram of the chitosan are effective in improving the mucoadhesive properties[22] and permeability of the chitosan polymer. If the thiol groups are reduced their immobilization can be determined by Ellman’s...
reagent, while if they are oxidized then by borohydride. Alternatively iodine titration method can be used[4].

**Effect on mucoadhesion**

Mucoadhesive properties of the chitosan are enhanced by 5-10 folds in case of thioglycolic acid conjugate and 10-20 fold in case of chitosan-4- thiobutylamidine conjugate[2, 23]. The main perspective of thiolation is to increase the mucoadhesion. Mucoadhesion of different polymers increase by many fold with the addition of thiol group (Table 2) [24, 25].

**Mechanism of mucoadhesion of thiomers[2]**

Mucin is present all over the mucus membrane which has cysteine rich domains. The thiol group interact with these cysteines and lead to formation of the disulfide bonds either by oxidation of the thiol groups or by thiol/disulfide exchange reaction (Figure 2).

![Mechanism of Mucoadhesion of Thiomers](image)

**Figure 2: Mechanism of Mucoadhesion of Thiomers**

The extent to which the mucoadhesion takes place depends upon the pKa of the thiol group, pH of thiolated chitosan and pH of the surrounding medium. The disulfide bonds thus formed are not influenced by the ionic strength and pH condition.

**In-situ gelling of chitosan[26]**

Ability of chitosan to crosslink adds more to its mucoadhesive efficiency. The chitosan, after forming surface interaction, it starts to form bonds with itself leading to more strong adhesion. The insitu gelling property of chitosan has been of great value for nasal, vaginal and other preparations[2].

Thiolated chitosan has shown more pronounced gelling property in comparison to unmodified chitosan. The thiol groups interact with each other leading to formation of more strong gel. This occurs due to oxidation of the thiol group at physiological pH. At pH 5.5, the sol-gel transition of the thiolated chitosan occurs after 2h. When the thiolated chitosan is rheologically observed for the gelling property, it has shown significant decline in the thiol group concentration showing
formation of disulfide bond formation. Also, thiolated chitosan show more elasticity in comparison. The insitu gel forming property of thiolated chitosan is important in case of liquid or semisolid preparation for nasal, vaginal or ocular use, where thin layer of solution is applied which form gelly layer on mucus and thereby increase the contact time and thus bioavailability of the drug in the body [2].

**Effect on permeation**

Thiolation of chitosan enhances its permeation effect more folds as compared to the simple chitosan. It can be assayed by using Ussing’s chamber, through the fresh intestinal mucosa. The studies have shown increase in the uptake of flouresenced bacitracin by 1.6 folds using chitosan cysteine, while for cysteine-TBA it has shown increase of cationic marker rhodamine 123 uptake by 3 folds as compared to unmodified chitosan[2].

**Mechanism of permeation enhancement**

Permeation enhancement effect of the thiolated chitosan can be explained by its effect on protein tyrosine phosphatase, the enzyme that is responsible for dephosphorylation of the transmembrane occludin tyrosine, the protein responsible for opening and closing of these tight junctions between cells. Thiolated chitosan inhibit this dephosphorylation to increase the permeation for drug, thus increasing bioavailability[2].

**Thiolated chitosan in different dosage forms**

**Microparticles**

Microparticulate dosage forms due to their small size have the ability to increase the bioavailability due to their increased time to stay in the body. Now when thiolated chitosan with improved mucoadhesive property and being more resistant to degradation is incorporated, the dosage form with more pronounced properties will be obtained[2]. Microparticles of thiolated polycarbophil were also prepared and shown to have 3 folds mucoadhesion as compared to unmodified polycarbophil[27].

**Tablets**

40% of all formulations are tablets. Thiolated chitosan can be incorporated for the prolonged release effect to the dosage form due to its insitu gelling properties. If only drug is mixed with polymer and compressed into tablet, it can still show zero order release for several hours. It shows hydration and diffusion account for the release rate[2].

**Solutions**

Thiolated chitosan seems to be unstable when in solution form due to its gelling property and disulphide bond formation within the polymer. This polymer used in solution formulations for eye can be effective in the most common eye problem, dry eye, the condition in which mucous
layer of eye acting as a surfactant becomes defective, there it can be used to form protective layer
to cope this condition[2].

Gels

Thiolated chitosan gel formulation seems to be very effective as compared to simple chitosan
gels due to the thiolated back bone which enhance its mucoadhesive properties[2].

Hydroxyethyl cellulose

Hydroxyethyl cellulose-cystamine is synthesized by open ring oxidative amination of the
hydroxyethyl cellulose to incorporate thiol groups on the polymer chain. The modified polymer
thus obtained has 3 fold more viscosity in comparison to the unmodified hydroxyethyl cellulose.
Also the swelling properties and the mucoadhesion is markedly improved[18, 28].

Anionic thiomer

Carboxylic acid group is present as the substrate in anionic thiomers. Presence of carboxylic
groups makes the immobilization of the thiol groups to these polymers more efficient by amide
bond formation in the presence of carbodimides. Examples include poly acrylic acid-cysteamine,
CMC-cysteine, alginate-cysteine (Table 1)[13].

Sodium alginate cysteine conjugate

Sodium alginate is thiolated for surplus effects. In the presence of carbodimidethiolation takes
place (Figure 3) and the thiomer thus produced is studied and shown to have 50% more viscosity
in comparison to the simple sodium alginate solution at 37\degree c. The swelling index is also
improved [29]. Tablets thus prepared by using this modified polymer has shown to be more
stable and resident on mucosa [11].
Poly acrylic acid cystamine conjugate

Poly acrylic acid cystamine conjugates are prepared in the presence of carbodimide by hydrolyzing polyacrylic acid polymer in demineralized water. Hydrolyzed polymer shows up its carboxylic acid group for S-S conjugation [30].

Polyacrylic acid homocysteine conjugates prepared in the presence of carbodimide have shown to contain sulfur 930 µmol ± 83 per gram of thiomer. Polyacrylic acid homocysteine has shown to have improved mucoadhesive characteristics as compared to unmodified polymer.
Sodium carboxy methyl starch (CMS) and carboxy methyl guar gum (CMG)[38]

Their thiomers are prepared in the presence of carbodimide by coupling reaction. Thiol groups in the form of cysteine are conjugated. Thereafter the mucoadhesive properties of both the polymers are studied which showed CMS to be less mucoadhesive then CMG. On the other hand the swellability of CMG is not effected by cysteine immobilisation. On the whole CMG proven to be better candidate as release of drug from the matrix tablet is 1.5 fold then CMS.

Thiolated xyloglucan

Xyloglucans are important glycans that are cellulose microfibers obtained from the seeds of the dicots. It is thiolated and its thiolation can be determined by Ellman’s reagent while mucoadhesive extent can be determined by in-situ gelling of the modified polymer[5].

Table 2: Thiomers with their effect on mucoadhesion[13]

<table>
<thead>
<tr>
<th>Thiomer</th>
<th>Increase in mucoadhesive strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan iminothiolane</td>
<td>250 times</td>
</tr>
<tr>
<td>Poly acrylic acid-cysteine</td>
<td>100 times</td>
</tr>
<tr>
<td>Poly acrylic acid-homocysteine</td>
<td>Approx. 20 times [43]</td>
</tr>
<tr>
<td>Chitosan thioglycolic acid</td>
<td>10 times</td>
</tr>
<tr>
<td>Chitosan thioethylamidine</td>
<td>9 times</td>
</tr>
<tr>
<td>Alginate cysteine</td>
<td>4 times</td>
</tr>
<tr>
<td>Polymethaacrylic acid-cysteine</td>
<td>Improved cohesiveness and mucoadhesion [44, 45]</td>
</tr>
<tr>
<td>Sodium carboxy methyl cellulose-cysteine</td>
<td>Increased mucoadhesion</td>
</tr>
<tr>
<td>Gallan gum-2-iminothiolane</td>
<td>Increased mucoadhesion [46]</td>
</tr>
<tr>
<td>Carbopol 980</td>
<td>Increased mucoadhesion [47]</td>
</tr>
<tr>
<td>Hyaluronicacid-L-cysteine</td>
<td>Increased mucoadhesion [48]</td>
</tr>
<tr>
<td>Carboxymethyl-Hyaluronic-Acid</td>
<td>Improved cohesiveness and mucoadhesion [49]</td>
</tr>
<tr>
<td>poly(ethyleneglycol)-glutathione</td>
<td>Improved drug delivery [50, 51]</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>Improved drug delivery [52]</td>
</tr>
</tbody>
</table>
Properties of thiomers

Hydrophilic properties of thiomers due to the thiol group make the polyacrylic acid and chitosan more mucoadhesive[13]. Other properties include cohesive properties, mucoadhesive properties, enzyme inhibition and permeation enhancement[7].

Characterization of thiomers[30]

Thiomers are tested and characterized for their stability and effectiveness by various methods such as

1. Determination of thiol group content[14]

The thiol group content on the polymer was determined by iodometry according to given procedure. The amount of thiol group tells the degree of thiolation. Hydrating with demineralized water thiomer was taken in the iodone flask. The pH of the solution was adjusted by adding 1 M HCl and then standard solution of 0.1N iodine was added and shook for 30 minutes. Excessive iodine was titrated with 0.1 N sodium thiosulphate solution. Sarch is used as an indicator.

Same procedure mentioned above is used for estimation of blank without thiomer. The degree of thiolation is determined by following formula.

\[
\text{% Thiol group content} = \frac{[(\text{Blank}-\text{Proper}) \times 0.1 \times 0.066 \times 100]}{0.1 \times \text{weight of thiomer}}
\]

2. Di-Sulfide bond formation[14]

200 mg of thiomer is hydrated with iodine in a flask and pH was adjusted between 2-3 using 1M HCl. Then 0.6 ml of 3% solution of sodium borohydride was added to the polymer and shaken for 15 min to hydrate all the disulfide bonds to free thiol groups. After this the mixture is neutralized by addition of 0.5 ml of 1M HCl. The thiomer before reduction and after reduction of thiol groups is subtracted to estimate disulfide content[31].

\[
\text{% Disulfide group content} = \frac{[(\text{B1-B2}) \times 0.1 \times 0.066 \times 100]}{0.1 \times \text{weight of thiomer}}
\]

3. Swelling behavior[14]

Thiomers prepared at different pH are compared. 30mg of thiomer was compressed into a disc of 5 mm diameter and dipped in demineralized water at 20°C by placing at permeable bottom tubes.

4. Viscosity[14]

The viscometer is used to measure the viscosity of thiomers. 2% solution is prepared and temperature conditions of 25±1 were used at 20 rpm.
5. Extent of mucoadhesion- in-vivo

The freshly excised intestinal mucosa of the sheep was taken to study the extent to which thiomer bind to the mucosa. The mucosa was clamped upside down and the exposed area was about $0.785\text{cm}^2$. Equal amounts of all formulations are used to equilibrate each part. Every sample mucosa was exposed for 2 minutes with formulation to ensure the intimate contact between the two. The weights are used to detach the mucosa clamped in the pan to another, the weights thus used to detach mucosa is expressed as detachment stress which will be used to estimate invivomucoadhesion of thiomer in dynes/cm$^2$.

$$\text{detachment stress} \left(\frac{\text{dynes}}{\text{cm}^2}\right) = \frac{m \times g}{A}$$

Where

$m=\text{mass}$

$g=\text{acceleration due to gravity}$

$A=\text{area of tissue exposed}$

**ROUTES OF DRUG ADMINISTRATION USING THIOMERS AS A CARRIER OF THE DRUGS**

There are various routes of drug administration that can be used to deliver the drug using thiomers as carrier. They have various applications using these routes of administration. The thiomer preparations are available for oral, nasal, ocular, buccal delivery of the drug. In literature, it is studied that thiomers can be used to deliver the drug through transmucosal route, gastrointestinal route, buccal route, oral route, nasal route, ophthalmic route and vaginal route of drug delivery. Different routes of drug administration along with the drugs that can be used through these routes are discussed as follows;

**Oral delivery of drug**

Oral route of drug administration is considered as the safe and effective for various drugs. Effects of various drugs can be enhanced when they are administered through oral route using thiolated polymers such as increased stay of drug in intestine and prolonged contact, enhanced permeation, enzyme inhibition [32]. Bioavailability of poorly bioavailable drugs like calcitonin, insulin and low molecular weight heparin can be increased using thiomers based formulations. There are various application of thiolated polymers in enhancement of bioavailability of poorly bioavailable drugs through oral route for examples;

Calcitonin; Calcitonin bioavailability is improved by conjugating it with the chitosan in modified form as compared to simple one due to the enzyme inhibiting and permeation enhancement effect[33]. It led to 5% more decrease in the calcium level[9].
Insulin: bioavailability and effect of insulin can be enhanced using thiolated polymer as the carrier in the form of matrix tablets. Thiolated Polycarbophil using cysteine was used to carry the insulin in the form of tablets. This formulation showed 36% more decrease in the blood sugar level comparatively [9].

Low molecular weight heparin: Low molecular weight heparin is administered subcutaneously which is painful and non-compliant thus there is a need for the development of the oral drug delivery system which will provide improved bioavailability. Thiolatedpoly (acrylic acid) was used as a carrier to deliver the LMW heparin orally. It was observed that formulating low molecular weight heparin with thiolated polymers have shown to provide relatively improved bioavailability (5.8±1.4%) [9]. LMW heparin has shown absolute bioavailability of ≥20% in rats[34].

Transmucosal delivery of drug

Thiomers have the potential to deliver the drugs through transmucosalrutes comparatively with better effects. Thiomers have the ability to provide the control drug release. In a study thiolated chitosan was prepared using thio butyl amidine as a conjugating agent. Chitosan-thio-butyl-amidine microspheres were prepared to evaluate the controlled delivery of the actives. The results have showed the controlled release of drug through these microspheres. Thus thiomers can be effectively used for the less absorbed drugs to be delivered transmucosally[35,36]. It is also concluded that the thiolated chitosan can be a good candidate for the formulation as beads for the controlled release of the drug[19].

Gastrointestinal delivery of drug

The recent advance in the polymer technology has led to improve in the drug delivery. The hydrophilic macromolecular drugs are now can be effectively delivered using thiomers due increased contact time by mucoadhesion and also due to enzyme inhibiting properties of thiomers as in case of GI peptidase[37].

Peptides:Peptide delivery can be enhanced by incorporating it with thiomers. The oxidation of peptide is reduced and also the permeation of drug through the gut is increased due to increased stay of the formulation in the body. Thiolated chitosan can enhance the stability and dissolution profile of the orally delivered peptides. One of the formulation for the oral delivery of peptides is by using the thiolated chitosan .i.e. chitosan-thio-butyl-amidine. It is compressed with tablets to deliver in gut. These tablets are coated with triglycerides to prevent adhesion in oral cavity or esophagus. In stated study enhanced bioavailability as well as stability was observed [38].

Buccal delivery of drug

Mucoadhesive buccal formulations are getting more and more intentions. Thiolated polymers can be effectively used to enhance the buccal delivery of drugs especially the drugs with problems
through trans GIT delivery of the drugs. L-cysteine conjugates were used to prepare the matrix tablets and there after the unmodified and modified polymers used in preparation are further studied for effect on mucoadhesion. Thiomers thus prove to be an effective excipient for buccal delivery of the drugs[39].

Nasal delivery of drug

Thiomers can also be effective carrier for the delivery of drug through nasal route. Enhanced mucoadhesion and permeation make the thiomers effective tool for the delivery of drug through this route. Nasal route has been shown to be effective for delivery of drug using thiomers as permeation enhancement effect is more prominent. Various thiolated polymers including chitosan, sodium alginites and polycarbophil can be used for the nasal delivery of the drug. Thiolated polycarbophil was used to study the leu-enkaphlin delivery on the bovine mucosal cells. The results showed to deliver the drug through the thiomer by sustained release and the degradation of drug is lowered. Also there was increase in drug uptake by nasal mucosa by 80 folds. Thus thiolated polycarbohil can prove to be a promising tool for nasal delivery drug[35].

Human growth harmone (hGH); Thiolated polycarbophil and glutathione was used for the delivery of hGH through nasal route in the form of hydrogel. It was observed that this formulation has effectively improve the plasma level of the drug [9].

Ophthalmic delivery of drug

Ophthalmic drug delivery is an effective route of administration but it also various drawbacks and the important one is decreased retention time of the drug. Various thiomers including thiolated chitosan, thiolated sodium alginate, thiolated poly ethylene glycol and polycarbophil etc. has the potential to deliver the drug effectively with increased mucoadhesion. A thiomer of non-ionic surfactant i.e. cysteine-PEG was used to formulate the nanoparticulate preparation of the cyclosporine to deliver through the ophthalmic route and was shown to remain in the ocular cul-de-sac for about 6h. Thus it has shown to increase the stay and also the concentration of drug in ocular region as compared to normal lipid carriers[40]. Similarly ocular inserts of using thiomers are carrier like thiolated polyacrylic acid can are also be formulated to improve the bioavailability as well as effectiveness of the drugs [35]. Various studies showed that plasmid DNA encoded with green fluorescence protein can be delivered with improved effects in a study, it was nanocomplexed with modified and unmodified chitosan to compare the effects of both carrier. Thereafter the transfection efficiency of thiolated chitosan and the sustained action produced by the thiolated chitosan was found greater comparatively [35,41].

Vaginal delivery of drug

Delivery of drug through intra-vaginal route using thiomers offer various advantages like increased in-situ gelling, controlled release, mucoadhesion, enzyme inhibition etc. thereby increasing the concentration of drug delivered. Thiomeric formulation to be administered
through vaginal route can be in the form of tablets, capsules, gels, liquids etc and once administered they remain there to deliver drug at a controlled release rate for even weeks[35].

In a study thiolated carbopol was used for vaginal delivery of LH-RH to observe the effect of thiomer on aminopeptidase N. it was observed that enzyme enhancement is greatly linked with thiol concentration. Increase in the concentration of thiol group improves the enzyme inhibition[42].

**Conclusion**

The improvement in the mucoadhesive properties of the polymers by incorporation of the thiol groups provide us with the polymers and ultimately, the dosage form with multiple additive properties such as taste masking, improved permeation, prolonged release, reduced irritation and patient compliance. Different polymers that are modified by addition of thiol groups, are used in different preparations for different routes accordingly. By using these modified polymers the plasma drug level are increased.
References


