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## Molecular aspects of muco- and bioadhesion: Tethered structures and site-specific surfaces

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### Abstract

Mucoadhesive controlled-release devices can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site. Acrylic-based hydrogels have been used extensively as mucoadhesive systems. They are well suited for bioadhesion due to their flexibility and nonabrasive characteristics in the partially swollen state, which reduce damage-causing attrition to the tissues in contact. Crosslinked polymeric devices may be rendered adhesive to the mucosa. For example, adhesive capabilities of these hydrogels can be improved by tethering of long flexible chains to their surfaces. Tethering of long poly(ethylene glycol) (PEG) chains on poly(acrylic acid) hydrogels and their copolymers can be achieved by grafting reactions, or by copolymerization in the presence of several PEG-containing acrylates. The ensuing hydrogels exhibit mucoadhesive properties due to enhanced anchoring of the chains with the mucosa. Theoretical calculations can lead to optimization of the tethered structure. Experimental results indicate that the chain interpenetration is a strong function of the PEG molecular weight, the polymer swelling ratio and the mucosa composition. © 2000 Elsevier Science B.V. All rights reserved.

*Keywords:* Hydrogels; Mucoadhesive; Interpenetration; Poly(ethylene glycol)

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### 1. Introduction

Mucoadhesion involves the attachment of a natural or synthetic polymer to a biological substrate. It is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. In recent years there has been an increased interest in mucoadhesive polymers for drug delivery [1,2]. Therefore, molecular design of the alteration and optimization of the adhesive characteristics of candidate materials for such applications has been a major part of our work.

The motivation for controlled drug release is the necessity to maintain a constant effective drug concentration in the body for an extended time period. For optimal performance, drug concentrations in the body should be maintained above the effective level and below the toxic level. However, when a drug is administered to a patient, the initial concentration of the drug in the body will peak above a toxic level before gradually diminishing to an ineffective level due to excretion. A mucoadhesive controlled-release device can improve the effectiveness of a treatment by helping to maintain the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids,

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and allowing targeting and localization of a drug at a specific site.

Mucoadhesion also increases the intimacy and duration of contact between a drug-containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The combined effects of the direct drug absorption and the decrease in excretion rate allow for an increased bioavailability of the drug with a smaller dosage and less frequent administration.

An advantage of using a mucoadhesive polymer carrier for drug delivery is the prevention of first-pass metabolism of certain protein drugs by the liver through the introduction of the drug via a route bypassing the digestive tract. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the bloodstream and not be inactivated by enzymatic degradation in the gastrointestinal tract [3]. A polymeric device allows for slow, controlled, and predictable drug release over a period of time and hence reduces the overall amount of drug needed.

Several polymeric bioadhesive drug delivery systems have been fabricated and studied in the past 20 years, not always with success. Several such devices are currently used in clinical applications involving dental, orthopedic, ophthalmological, and surgical uses. Viable application sites include the mouth, intestine, nose, eye, and vagina. Acrylic-based hydrogels have been used extensively for bioadhesive devices. Acrylic-based hydrogels are well-suited for bioadhesion due to their flexibility and nonabrasive characteristics in the partially swollen state which reduce damage-causing attrition to the tissues in contact [4]. Furthermore, their high permeability in the swollen state allows unreacted monomer, uncrosslinked polymer chains, and the initiator to be washed out of the matrix after polymerization. Acrylic-based polymer devices exhibit very high adhesive bond strength [4–6].

## 2. Polymer–polymer interdiffusion and adhesion

The theories of polymer–polymer adhesion can be adapted to polymer–tissue adhesion or bioadhesion by recognizing that bioadhesion is different only

because of the differing properties of the tissue as opposed to those of the polymer. Numerous theories have been developed to explain the phenomenon of bioadhesion. No individual theory has been universally accepted as the singular mechanism by which bioadhesion occurs, though a combination of theories may be used to describe the phenomenon. The adhesion theories include electronic theory, wetting theory, adsorption theory, and diffusion theory.

According to the electronic theory, there is a double layer of electrical charge at the interface between the bioadhesive and the tissue, due to a transfer of electrons upon contact. This electron transfer occurs because of the difference in structure between the bioadhesive and the glycoprotein chains in the mucus. Bioadhesion in this case is due to an attraction across the electrical double layer [7].

The adsorption theory has been developed over a period of many years and suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding [8]. The fracture theory of bioadhesion relates the force necessary to separate two surfaces to the adhesive bond strength.

The wetting theory, which applies mainly to liquid bioadhesive systems, analyzes the ability of a paste or liquid to spread over a biological surface [9]. This theory uses analysis of the spreading coefficient of a liquid bioadhesive over a tissue by displacement of the surrounding gastric fluid. Good and Giffalco [10] offered the calculation of the interfacial tension between the bioadhesive liquid and the tissue. It was later shown by Helfand and Tagami [11,12] that the interfacial tension was proportional to  $\chi^{1/2}$ , where  $\chi$  is the Flory polymer–polymer interaction parameter. Low values of this parameter correspond to structural similarities between polymers and an increased miscibility.

The diffusion theory was proposed by Voyutskii [13] and involves interpenetration of the polymer chains in the interfacial region as illustrated in Fig. 1. In bioadhesion, the polymer is first brought into intimate contact with the mucus, and, over time, the concentration gradient across the interface causes the diffusion of the chains of the bioadhesive into the mucus layer and also the diffusion of the glycoprotein chains of the mucus into the bioadhesive polymer. The rate of the diffusion is dependent on the chemical potential gradient and the diffusion coeffi-

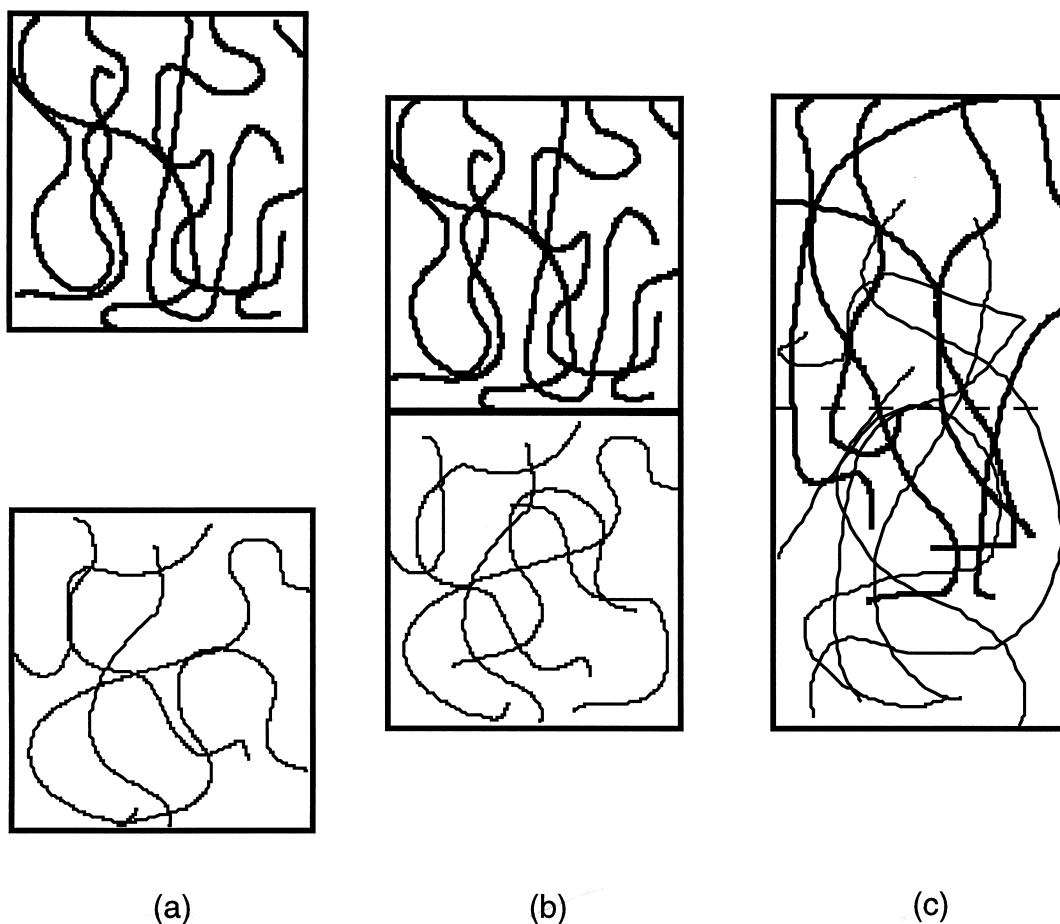


Fig. 1. Schematic representation of diffusion theory of adhesion. (a) Top layer and bottom layer before contact; (b) top layer and bottom layer right after contact; (c) top layer and bottom layer after contact for a period of time.

cient of a macromolecule through a crosslinked network. The chains that have diffused across the interface serve as anchors to aid in securing semipermanently the bioadhesive device in place. The interpenetration distance necessary for good bioadhesion is approximately equal to the end-to-end distance of the macromolecular chains.

### 3. Molecular understanding of mucoadhesive promoters behavior

Theoretical and experimental evaluation of the

diffusion theory of adhesion, especially for uncrosslinked polymer melts, has been the focus of substantial research. Interpenetration of polymer chains across the interface can result in adhesion. The intimate contact of the two substrates is essential for diffusion to occur; the driving force for the interdiffusion is the concentration gradient across the interface. The two phases must be compatible. These criteria are most likely fulfilled when the two phases have similar chemical structures.

In the case of a gel system, it is the chain ends and smaller molecular weight chains that contribute to the interpenetration process. Molecular understanding of gel–gel and gel–mucin adhesion can lead to

better understanding of the behavior of such systems. Based on the interdiffusion theory of adhesion, an important contributor to good adhesion is the presence of molecular *adhesion promoters* such as polymer-tethered structures (e.g., poly(ethylene glycol) [PEG] chains grafted to crosslinked networks) or even linear chains which are free to diffuse across the gel–gel interface. The idea of the use of adhesion promoters to achieve improved bioadhesion is relatively new and was first proposed by our laboratory in the work of DeAscentiis et al. [14]. This method has been examined for possible use in novel buccal, transmucosal and vaginal drug delivery systems.

The idea that free and tethered chains in the interface region can be used to enhance adhesion has been studied in the dry network cases such as rubber–rubber adhesion and rubber–solid adhesion. Brochard-Wyart and de Gennes [15] came up with a scaling analysis for the interdigitation between a polymer brush and a rubber network. Their results suggested that the adhesion strength enhanced by the tethered chains would first increase with the surface coverage, and then decrease after a specific value of surface coverage. The experimental results by Leger and Raphael [16] qualitatively proved that prediction. For a recent review on the theoretical and experimental results about this field, see Ref. [17].

Though the effect of the adhesion promoters in dry polymers has been studied and proven, their role in the solution case still deserves more investigation. As a starting point, researchers draw analogies with the case of tethered chains on dry polymers. However, care must be taken to distinguish the differences between bioadhesion and normal polymer–polymer adhesion. In the latter case, use of external forces to bring the two polymer surfaces in contact in order to achieve an adhesive bond is accepted. On the other side, in bioadhesion, as for example in oral, vaginal or rectal adhesion to the mucosa, no external forces can be applied. Therefore, any unfavorable free energy changes caused by adhesion promoters related to the approach of the polymer to the mucosa are undesirable here.

Chain interpenetration is clearly a mechanism contributing to bioadhesion [20]. The dependences of the diffusivity on system parameters such as molecular weight, degree of crosslinking and the degree of

swelling are important if diffusion can be manipulated to enhance bioadhesion [1]. Our research group has been in the forefront of development and investigation of the molecular and pharmacological behavior of new bioadhesive carrier materials for drug delivery applications.

Studies were performed in our laboratories by DeAscentiis and coworkers [14,18] and Achar and Peppas [19] who investigated a number of poly(acrylic acid) (PAA) and poly(2-hydroxyethylmethacrylate) microspheres of varying degrees of crosslinking and found little dependence of mucoadhesion on the degree of crosslinking. However, in the work of DeAscentiis et al. [14] we found that if we incorporated free PEG chains in the particles, mucoadhesion was improved significantly because of the penetration of the free PEG chains across the mucosa–polymer interface. We believe that this is the first reference of use of adhesion promoters (more specifically PEG) for mucoadhesive drug delivery systems. Fourier transform infrared (FTIR) spectroscopy and microscopy were developed in our laboratory to study mucoadhesion of various polymers. Successful application of FTIR and attenuated total reflectance FTIR techniques led to unequivocal determination of the mucoadhesive behavior of PAA and other systems as indicated by Jabbari et al. [20].

Adequate solubility of the bioadhesive in the mucus is also essential for good bioadhesion. Consequently, the solubility parameters of each substance must be similar, which can be achieved by creating a bioadhesive device that is of similar chemical structure as mucus. Thus, polymers containing hydroxyl, carboxyl, and some amines and sulfates make good bioadhesive devices. Other structural aspects found to favor good mucoadhesion are good diffusion and entanglement between the bioadhesive device and the mucus, and a polymer molecular weight that is high enough, but does not exceed a certain value. If the polymer chains are too long, their ability to diffuse is limited.

In our present work, we address the use of *adhesion promoters for the enhancement of mucoadhesion*. Our goal is to examine both the macroscopic adhesive properties of synthetic hydrogels and the impact of polymer chain diffusion

(adhesion promoter diffusion) on the adhesion of gel–mucin systems.

#### 4. Tethered PEG chains and mucoadhesion

Tethered polymer chains are polymer chains with one of their ends attached on a  $d$ -dimensional surface [21], where  $d=1$  denotes comb polymers, and  $d=2$  denotes normal, flat surfaces. The polymer chain tethered structures have been extensively studied since the pioneering works of Alexander [22]. The behavior of tethered structures on solid surfaces is well understood. Thus, such systems have found numerous applications.

Though tethered structures attached to dry polymer systems have long been used to enhance the adhesion strength between rubbery polymers and another solid [20], tethered structures in solutions are traditionally used for antiadhesion purposes, such as colloid stabilization and protein adsorption resist-

ance. However, all previously studied tethered systems, whether in a dry or a solution environment, are tethered on solid surfaces. Our area of interest involves hydrogel surfaces, which are basically different from impenetrable solid surfaces.

As illustrated in Fig. 2, in our work we want to exploit tethered chains on hydrogel surfaces as bioadhesion promoters. Although the diffusion coefficient of tethered chains is lower than that of the free chains at interfaces due to their geometric constraints [23], they still have a significant ability to penetrate into the network. Tethered chain adhesion promoters have the following advantages as compared to free chains.

1. They have one of their ends covalently bonded with the hydrogel. Thus, we can expect that possible adhesion strength enhancement would be higher than that of the free loaded chains.
2. The amount and length of tethered chains are easier to control.

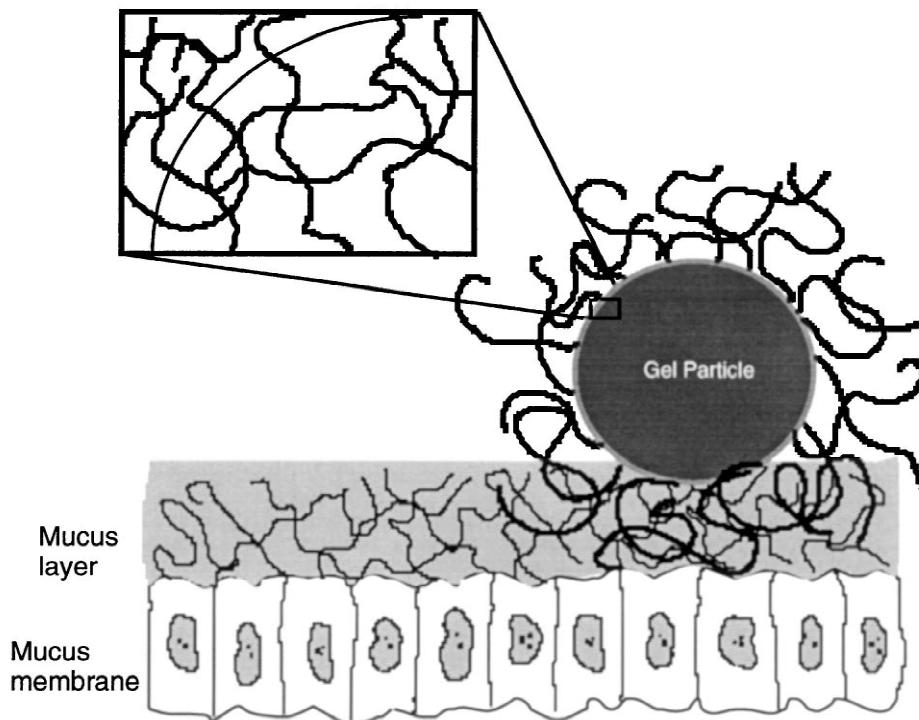


Fig. 2. Schematic diagram representing the interpenetration between tethered chains and mucus gel layer.

3. We can obtain tethered hydrogel surfaces by a grafting reaction after the hydrogels have been prepared. Consequently, we need not change the bulk properties of the hydrogel, which can be designed separately.

We wish to emphasize that the main function of the tethered chains on hydrogel surfaces is to extend the adhesion phenomena to a thicker interface region. Although they may form entanglements with the mucin network, long tethered chains are not perfect. Indeed, the longer the tethered chains, the longer time they need to penetrate into the mucus gel layer. In some cases, the time scale may be beyond the turnover time of the mucus layer itself.

### 5. Site-specific and tethered structures

A key factor in promoting adhesion would be the ability of a matrix to have units that are specifically designed to adhere to a given surface. It is a commonly known fact that certain amino acid sequences have complementary parts on cell and mucosal surfaces. Thus amino acids sequences such as Arg–Gly–Asp and others, if attached to the matrix, could promote adhesion by binding with specific cell surface glycoproteins. Even more useful would be the ability to selectively adhere to diseased tissues. Certain diseases cause changes in cell surface glycoproteins. In turn, these altered protein sequences could be targeted by amino acid sequences on a drug delivery device. The device would bind to most cells, but would bind with a higher affinity to diseased cells. The problem at this point is finding these glycoproteins and how they change once they are diseased.

These protein sequences would probably be most effective if they were tethered to the matrix surface, so that they have the highest mobility possible. Thus, they can attain the largest area of interaction. PEG is an excellent candidate for such a function. The long chains of the higher weight molecules could allow the amino acid sequence attached to the PEG chains ends to move relatively freely in the surrounding medium, thus giving it a higher chance of locating and binding to mucosal or cell surface glycoproteins. Using PEG might create a problem though, because

PEG is often used for its stealth characteristics and adding amino acid sequences to the end of these chains might cause the PEG chains to be easily recognizable by the body's immune system.

### 6. Preparation of adhesion-promoted hydrogel systems

Adhesion promoting polymer chains can be introduced into a hydrogel system either by free loading or by chemical grafting. Hydrogel systems loaded with free polymer chains can be produced by addition of chemically inert polymer chains into the monomer mixtures before the polymerization process. For example, a useful system can be produced by photopolymerizing a mixture containing acrylic acid, crosslinking agent, photoinitiator, and PEG chains. The latter will not react with the acrylic acid in this case. The advantage of this method is that the PEG chains can be introduced into the hydrogel in one step, however the free chain can be washed out of the hydrogel system.

Tethered polymer chains as adhesion promoter can be produced by grafting the polymer chain on a hydrogel system or copolymerizing a polymeric system with specific monomer that will contribute to the tethered structure. The most widely used methods to graft polymer chains onto a hydrogel surface are condensation and free radical polymerization. For example, hydroxyl terminated PEG can be grafted by condensation polymerization onto a hydrogel surface which contains carboxyl functional groups. High-energy beams like gamma rays can be used to irradiate the hydrogel surface to create radicals that can initiate free radical polymerization with acrylated monomers.

Various monomers can be copolymerized to produce tethered hydrogels. For example, PEG monomethyl ether methacrylate can be copolymerized with acrylated monomers to produce PEG-tethered hydrogels. This method is very attractive as it can produce a hydrogel with tethered chains in one polymerization process. This method can also achieve a hydrogel system with high density of PEG-tethered chain. However the high density of these PEG-tethered chains provides tremendous steric hindrance to the system, especially when the

PEG chains accommodate a mushroom conformation. This steric hindrance prompts the monomers to form short polymer chains that contribute to fewer physical crosslinks in the network system, thus resulting in low mechanical strength. Adding more chemical crosslinks into the system leads to a stronger three-dimensional network structure but also increases the fragility of the network. Adding spacers between the PEG-tethered chains allows the monomers to form a longer polymer chain, thus increasing the mechanical strength of the hydrogel network.

Hydrogels with high density of PEG-tethered chains are very important as biomaterials and for drug delivery applications. The high density of PEG-tethered chains can provide numerous anchors to sustain adhesion. It will also provide a good protection for sensitive drugs, such as therapeutic proteins. The ability of such a hydrogel to inhibit platelet and protein adhesion while showing stealth behavior is very attractive for biomaterials.

## 7. Theoretical predictions

As polymer-tethered hydrogel surfaces approach the mucus surface, the tethered chains contact the mucus first. Their effect on the adhesion strength is determined by whether they diffuse into the mucus and how they behave in the interface region.

The diffusion process is thermodynamically controlled by the free energy change of the whole system when the hydrogel and mucus approach each other. The free energy change includes osmotic repulsion, entropy contribution from tethered polymers, and interaction among the tethered polymer and the gel polymers. If the sum of these terms is negative, the tethered chains will diffuse into the mucus spontaneously and the hydrogel carrier will adhere to mucus.

We have conducted a molecular thermodynamic study based on single-chain mean-field theory. With this study we can analyze the approach process of a tethered hydrogel to the mucus layer. In these preliminary studies, we consider both the drug-containing hydrogel and the mucus as homogeneous, three-dimensional random arrays of constituted polymer segments, while their interface is taken as uniform and flat.

We have systematically studied the effect of tethered structures on the gel–mucus adhesion process. Typical results of the free energy analysis of the process are shown in Fig. 3. The interaction between the hydrogel and mucus can change from purely repulsive to purely attractive, by only changing the interaction between the tethered chains and mucus. Moreover, from the thermodynamic analysis of the adhesion process, the repulsion is mainly due to the osmotic pressure increase when the hydrogel and mucus are in intimate contact. On the other hand, attraction between tethered polymers and mucus can overcome the energy barrier and render the adhesion spontaneous. Notice that the repulsion is not related to the detailed chemical structure, although the attraction needed for mucoadhesion is sensitive to the properties of tethered chains. Therefore, the desirable site-specific drug delivery may be achieved by specifically designing tethered structures on the hydrogel surfaces without changing the bulk structures of the hydrogel. This can be separately optimized for controlled release properties.

## 8. Mucoadhesion measurement

The gels investigated here were grafted copolymers of PEG monomethacrylate with methacrylic acid (MAA) containing a 1:1 molar ratio of the two components. They were placed in a tensile tester (Instron) at 25°C and 90% relative humidity. The samples were adhered to the upper holder of the tester, whereas a sample of gelled bovine submaxillary mucin was placed on the lower jaws. The two jaws were brought together for 15 min and then separated at 1 mm/min. The detachment force was measured as a function of displacement. The work of fracture, equivalent to the work of bioadhesion, was calculated as the area under the curve.

Fig. 4 shows the mucoadhesive behavior of these systems. In the hydrogels tested, P(MAA–g-EG), there were tethered PEG chains at the interface region. The detachment force was plotted versus displacement for mucin adhesion of pH values of 3.2 and 7.4. The work of adhesion was significantly higher at the pH value of 7.4. This indicated that the tethered PEG chains acted as anchors for the mucoadhesion observed at those conditions, because

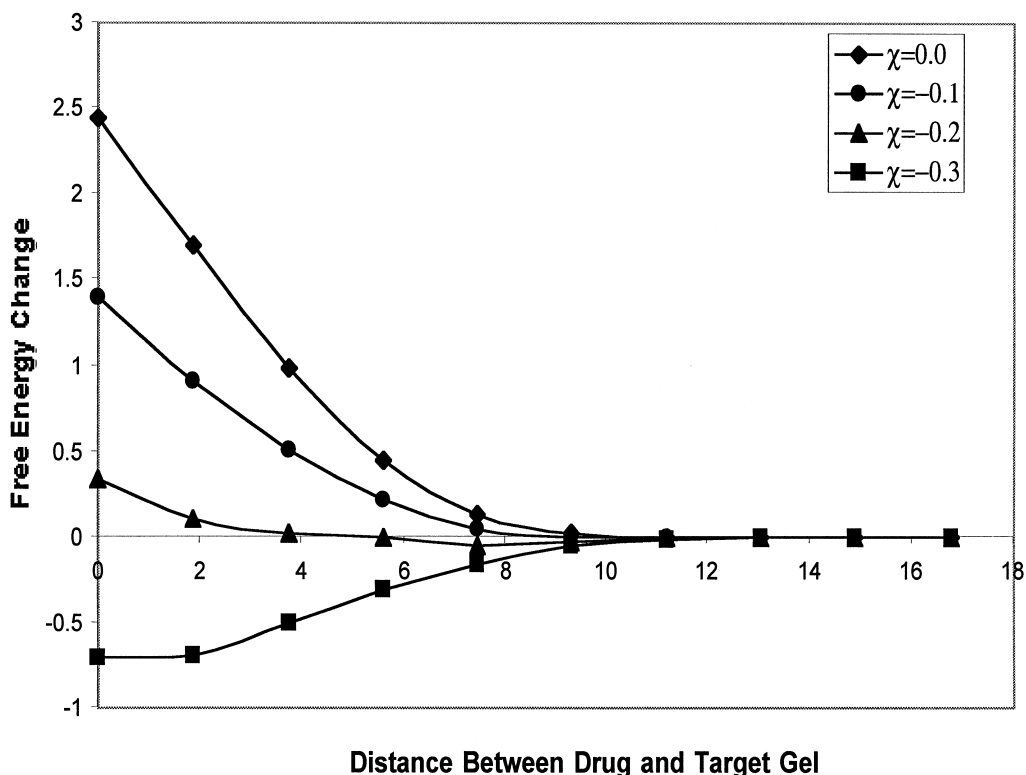


Fig. 3. Free energy change during the approach process of a tethered structure to a gel, where  $\chi$  is the interaction parameter between the tethered polymers and the target gel. No other type of interaction is included. The tethered chain length contains  $n=20$  segments, the surface tethered density is  $\sigma=0.1$ , and the target gel polymer volume fraction is  $\phi=0.1$ .

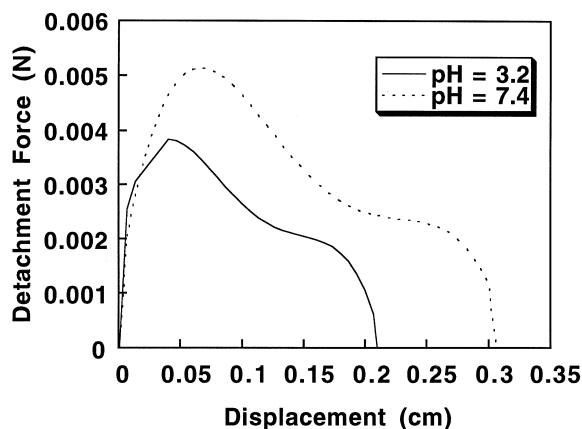


Fig. 4. Adhesive behavior of P(MAA-g-EG) gels at pH values of 3.2 and 7.4 in contact with bovine submaxillary gland mucin.

otherwise the adhesion strength should be higher in the low pH case where the carboxyl group remains in the acid form and can contribute to mucoadhesion by hydrogen-bonding [5].

These studies are indicative of the strong effect of a mucoadhesion promoter and verify the theoretical studies presented here.

## 9. Conclusions

In this paper, we analyzed the idea that polymer chains tethered on hydrogel surfaces may have important applications in drug delivery fields, such as mucoadhesion promotion and site-specific drug targeting. The advantage of tethered structures is the ability to modify the surface properties of hydrogel systems, which is important for bioadhesion and site-specific targeting, while its bulk properties re-

main unaffected which can be optimized separately for controlled release.

Theoretical calculations showed that the tethered surface could be modified to optimize adhesion, and in turn to achieve a better drug delivery device. These preliminary calculations showed that this approach is encouraging.

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