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Novel mucoadhesive system based on sulfhydryl-acrylate interactions

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Abstract We propose a novel cross-linked mucoadhesive system that can interact covalently with mucin type glycoprotein, thus providing both strong bonding to mucosa as well as ability to function as a sustained release matrix. The strong bonding results from Michael type addition reaction between an acrylate end group on a polymer and the sulfide end group of the mucin type glycoprotein. A proof of concept is provided using a polyehtylene glycol hydrogel formed in situ from polyehtylene glycol di-acrylate (PEG-DA) macromers. The ability of PEG-DA to create interactions with mucin type glycoproteins was verified using nuclear magnetic resonance (NMR) and rheology experiments. NMR studies have detected disappearance of the PEG-DA's vinyl protons upon mucin addition, whereas rheology measurements have shown a viscosity increase. These results provide an evidence for the formation of mucin-polymer covalent bond. The ability PEG-DA to attach to mucus and promote mucoadhesion was evaluated by tensile measurements. PEG-DA adhered at strength comparable to other covalently interacting mucoadhesive polymers. Furthermore, PEG-DA was found to be a suitable candidate for sustained release of the hydrophilic drug Ibuprofen.

1 Introduction

Mucoadhesive drug delivery vehicles offer some benefits over other delivery methods including extended residence time of the drug at the site of application, a relatively large permeability of the mucous membranes that allows rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of part of the body's natural defense mechanisms [1, 2]. Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element in the design of these drug delivery systems [1, 2]. The mucus layer covers organs that are exposed to the outer surface of the body yet are not covered with skin, such as the mouth and the respiratory tract. It is composed of 95% water and about 5% mucus glycoproteins, termed mucin, plus a large number of minor components [3]. The mucin type glycoproteins contain several sulfide domains in addition to carboxyl terminal group domains [4, 5].

Several classes of polymers have been proposed as mucoadhesives due to their ability to interact physically and/or chemically with the mucus [1]. Non-covalent bonds such as hydrogen bonds, Van-Der Waals forces, ionic interactions and/or chain entanglements are the most common polymer-mucus bonds [6]. However, attempts have been made to improve the mucoadhesive properties *via* covalent linking such as disulfide bonds between the polymer to the mucin type glycoproteins [7–11]. This approach has lead to the development of thiolated polymers, also termed thiomers, in which a small molecule (ligand) consisting a thiol functional group is attached to the polymer chain [7–10]. Although dry carriers prepared from thiomers display high adhesion to mucus, our previous study [12] has shown that mucoadhesive system based on alginate-thiol molecules were not able to display their advantages in hydrated environment. The benefit achieved by adding thiol groups to the polymer seemed to be flawed in the hydrated cross-linked form due to the formation of inter-molecular di-sulfide junctions.

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In order to overcome this limitation, a novel mucoadhesive system is proposed in this study. It is based on the ability of molecules carrying electronegative vinyl end group to covalently attach to electronegative neighboring groups, in a reaction termed Michael type addition, which can take place in physiological environment. Here we utilized a form of this reaction developed by Hubbell and co-workers [13, 14] for conjugating sulfhydryl-containing bio-molecules such as peptides or proteins with unsaturated groups such as vinyl-carrying polymers. This methodology was further developed for the modification of many hydrogel systems such as poly(vinyl alcohol) [15], poly(ethylene glycol)-*b*-poly(lactic acid) [16] and PEGylated products [17, 18].

For our initial studies we have chosen polyehtylene glycol di-acrylate (PEG-DA). Polyehtylene glycol (PEG) has been previously proposed as an adhesive material due to its ability to create hydrogen bonds with sugars residues on glycosylated proteins [19–21]. Moreover, adding linear PEG chains to hydrogel matrices enhanced their adhesion to the mucus due to chain interpenetration at the hydrogel/mucus interface [22–26]. Previous work by Selikter and co-workers [18] has shown that although pure PEG-DA hydrogels do not promote cell growth inside of them these materials are not toxic to human cells. The underlying hypothesis of the current study was that the ability of acrylate chemical end groups to covalently associate with sulfide end groups under mild conditions could be used to chemically attach molecules carrying such groups to the mucus, thus enhancing the mucoadhesive properties even further. To examine this hypothesis we first verified the formation of covalent bonds between PEG-DA and mucin using nuclear magnetic resonance (NMR) and rheology experiments. In addition, the adhesion to fresh tissue and drug release ability were characterized. To the best of our knowledge the use of acrylate in general, and PEG-DA in particular, was not suggested before as a means of creating mucoadhesive system.

2 Materials and methods

2.1 Materials

Polyethylene glycol (PEG) with molecular weight of 10 kDa was purchased from Sigma and used as received. PEG-DA was synthesized according to a previously published procedure [18]. Irgacure 2959 (Siba) was used as initiator. Alginate HF120RBS was kindly provided from FMC biopolymers, Norway. Alginate-thiol was synthesized as described before [12]. Mucin was extracted from fresh porcine small intestine and lyophilized by drying frozen aqueous solutions at −30°C at 0.01 mbar. The final product was stored at 4°C until further use.

Porcine small intestine samples were kindly donated by the "White Meilia" slaughterhouse (Meilia, Israel). Samples were used fresh, and tested within 24 h. Intestine samples were cut open, spread on a petri-dish and kept covered in order to eliminate contamination and prevent drying. Washing was avoided in order to preserve the mucus layer.

2.2 Nuclear magnetic resonance

The interaction between PEG-DA and mucin's glycoproteins was investigated using ^{1}H NMR spectra. 20 mg/ml PEG-DA and 20 mg/ml mucin was dissolved in D_2O a day before the experiment. The same concentrations were used for the control experiments where each of the components was dissolved separately in D_2O.

Proton NMR spectra were acquired on a Bruker Avance 500 spectrometer operating at 500.13 MHz, equipped with a Bruker bbo-z-gradient probe, at a constant temperature of 25°C. Typical acquisition parameters for ^{1}H spectra were: 5500 Hz spectral width, 32 k real points, 21 kHz B1 field, signal averaging of 64 transients and relaxation delay of 3 s. Spectra were typically processed with zero-filling and without window functions. To suppress the large water signal, the standard Bruker 3-9-19 watergate pulse sequence [27, 28] with z-gradients was used with the water signal on resonance.

2.3 Rheology

The dependence of the viscosity on the shear rate was evaluated using Advanced Rheometric Expansion System (ARES) instrument. The experiments were performed using a Cone and Plate geometry having a 50 mm radius at constant temperature of 25°C. Rate sweep experiments were performed at shear rates in the range of 10–100 s^{-1}. Solutions containing either PEG-DA or PEG (20 mg/ml) and mucin (20 mg/ml) were used. The samples were dissolved in distilled water and the measurements were performed approximately 1 h after dissolution.

2.4 Assessment of the mucoadhesion properties

Mucoadhesion properties were characterized using a new technique developed in this study. The methodology was designed to allow evaluation of the adherence ability of cross-linked networks in wet environment. Furthermore, the experimental setup allows the cross-linking reaction to occur on the adhesion surface. A fresh small intestine surface was placed on a 25 mm stainless steel grid connected to vacuum system, which attached the lower surface of the tissue to the grid without the need to used glues or other chemicals. Since the upper surface of the tissue was

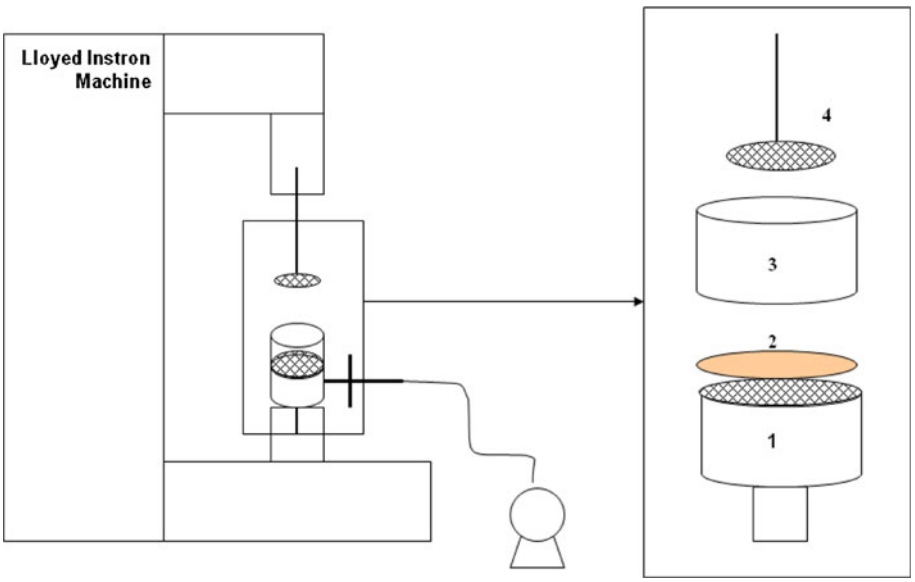

Fig. 1 Schematic illustration of the instrument for assessment of bioadhesion. *1* lower apparatus arm which connected to the vacuum system, *2* the mucus tissue, *3* polyethylene mold and *4* stainless steel grid connected to the upper instrument arm

not exposed to vacuum, the naturally occurring mucus surface was not dehydrated. This 25 mm grid was then fixed to the lower arm of a Lloyed Tensile machine equipped with a 50 N load cell. A long stainless steel rod attached to a smaller stainless steel grid, 18 mm in diameter, was fixed to the upper arm of the tensile machine (Fig. 1). A polyethylene pipe with a 25 mm inside diameter was placed on the tissue to serve as a mold, and 3 ml macromer solution was poured into it. Immediately after, the upper arm carrying the smaller grid was slowly lowered into the mold until the grid was fully immersed and centered in the macromer solution. Then, the cross-linking reaction was induced by shining the solution with UV light from a spot source. The upper grid remained connected to the upper arm of the instrument throughout the cross-linking process. The cross-linking reaction resulted in hardening of the macomer solution and a firm attachment of the upper grid to the gel. Finally, the polyethylene mold was removed. In order to measure the maximum adhesion force, the machine was set to an extension mode were the upper arm was pulled at a constant rate of 1 mm/min and the force was recorded until detachment was observed. The fresh mucus surface was replaced before each test. The maximum adhesion forces are the average of twelve measurements ($n = 12$) for PEG-DA samples and three measurements ($n = 3$) for alginate-thiol and the 2% pre-geled PEG-DA. The confidence intervals were determined at 0.05 significance level.

2.5 Drug release

Release studies of the hydrophilic model drug Ibuprofen were conducted with various PEG-DA hydrogels. Ibuprofen is a non-steroidal anti-inflammatory drug used in the commercial products Advil® (Wyeth Inc.) and Nurofen® (Reckitt Benckiser Inc.) (Fig. 2).

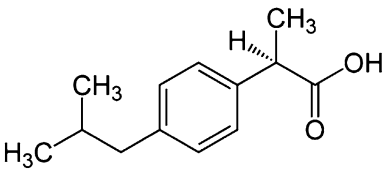

Fig. 2 The chemical structure of Ibuprofen

Gel tablet (600 µl) was placed in 50 ml Phosphate buffer 50 mM pH 7.4. Aliquot from the dissolution medium were withdrawn periodically and analyzed using Bio-Tek, Inc. UV spectrophotometer at a wavelength of 234 nm. Samples for release studies were prepared by cross-linking a solution containing 1% (w/w) Ibuprofen in varied PEG-DA concentrations and 15 µl/ml initiator solution (100 mg/ml Irgacure 2959 in 70% ethanol–water solution). PEG-DA tablets without drug were used as blank. Pre-gel samples were exposed to UV radiation for 5 min in order to induce cross-linking. The drug concentration was determined using calibration curves of Ibuprofen at 234 nm.

3 Results and discussion

3.1 PEG-Da/mucin interactions

Oxygen coupled vinyl end groups are known for their ability to interact with other electronegative end groups such as sulfides. In this reaction, termed Michael type addition, the reactive double bond is opened and creates a new covalent bond between the two components. Our hypothesis was that

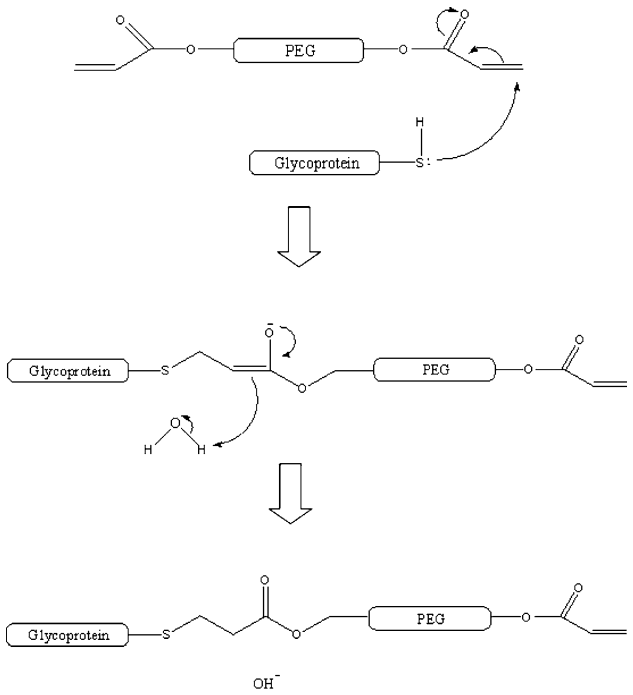

Fig. 3 Schematic illustration of Michael type addition between PEG-DA molecule and a glycoprotein's thiol end group

Michael type addition reaction could be utilized to chemically attach PEG-DA to the mucus (see Fig. 3).

The ability of PEG-DA molecules to interact covalently with mucin content according to the Michael type conjugation was first monitored on the molecular level using NMR then on the macroscopic level using rheology and adhesion measurements.

Figure 4 compares NMR spectra of native PEG-DA, mucin, and a spectrum obtained from their mixture. The spectrum obtained from native PEG-DA (Fig. 4a) reveals several peaks located at $\delta = 5.9$–6.5 ppm which can be ascribed to the vinyl end group protons. Moreover, the repeating unit (methylene) protons were also detected at $\delta = 4.3$ and at $\delta = 3.6$. The other two peaks located at $\delta = 3.1$ and at $\delta = 1.2$ are suspected to be a remnant from di-acrylate addition reaction.

The peaks at $\delta = 5.9$–6.5 ppm, which belong to the vinyl end group, were also detected in the spectrum from the mucin/PEG-DA mixture (Fig. 4b) however their intensity decreased suggesting that some of the vinyl bonds disappear due to glycoprotein addition. It is known that changes in electron environment due to double bond opening allude to peak disappearance. Moreover, new protons were found in the low ppm region where $-CH_2$ groups are usually located. These findings support the hypothesis that PEG-DA potentially created intermolecular interactions with mucin glycoproteins. It is important to emphasize that the NMR results are quantitative because the experiments were performed using the same polymer concentration and all samples were kept under the same conditions and prepared at the same time. In addition, the NMR measurements were performed in a comparable conditions were the molecules sustained relaxation during the NMR pulse program.

In order to further verify the existence of interactions between the PEG-DA and the glycoprotein, rheology measurements were performed. Previous works in the field of mucoadhesive polymers have attributed viscosity

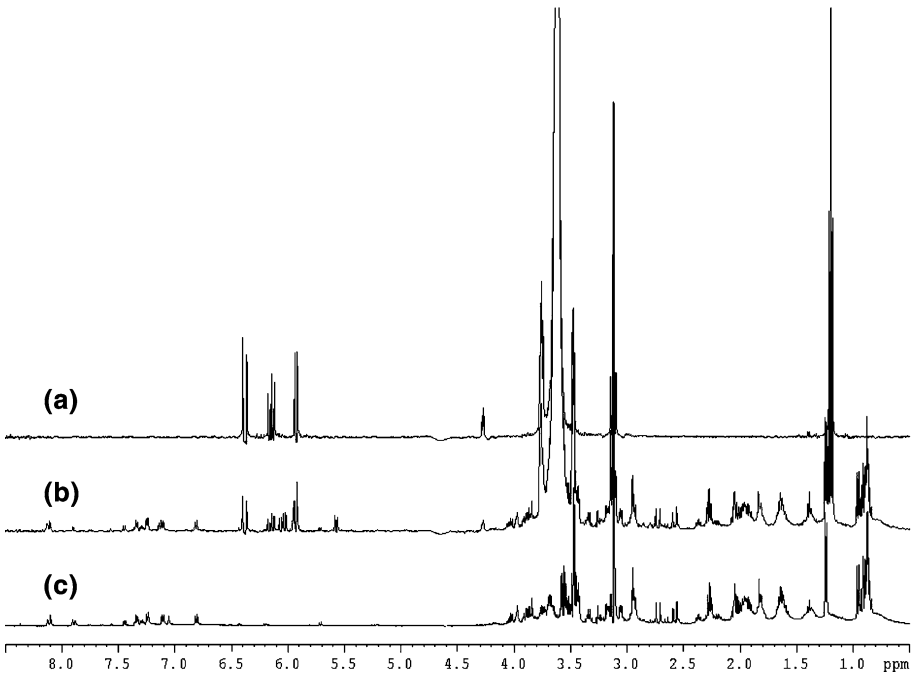

Fig. 4 NMR spectra of (*a*) PEG-DA, 20 mg/ml, (*b*) a mixture of PEG-DA (20 mg/ml) and mucin (20 mg/ml) and (*c*) mucin, 20 mg/ml in D_2O

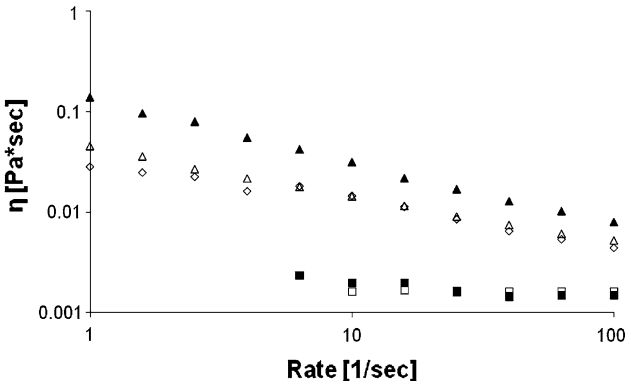

Fig. 5 Rate sweep experiment of (*open diamond*) mucin 20 mg/ml, (*filled square*) PEG-Da 10 kDa 20 mg/ml, (*open square*) PEG-OH 10 kDa 20 mg/ml, (*filled triangle*) mucin 20 mg/ml + PEG-Da 10 kDa 20 mg/ml and (*open triangle*) mucin 20 mg/ml + PEG-OH 10 kDa 20 mg/ml in distilled water at 25°C

enhancement after mucin addition to molecular interaction between the polymer and glycoprotein [7, 29]. Similar behavior can be observed in Fig. 5, where addition of mucin to PEG-DA has led to a viscosity increase. It should be noted that addition of relatively high molecular weight glycoprotein to polymer solution could increase its viscosity even in the absence of specific chemical interactions, due to the formation of additional entanglements as a result of a concentration increase. Therefore, a control experiment in which PEG-OH having the same molecular weight as the PEG-DA was mixed with the mucin was performed. PEG-OH is polyethylene oxide consisting of the same repeating unit as PEG-DA however carries a hydroxyl end group rather than acrylate. As can be seen in Fig. 5, a mixture of PEG-OH and mucin displays a lower viscosity than the mucin/PEG-DA mixture. This result supports the suggestion that PEG-DA interacts with the mucin glycoproteins. We suggest that those interactions are a result of Michael type addition reaction between the PEG-DA's acrylate end group and glycoprotein's sulfide end group, since this is the only possible interactions which cannot occur when PEG-OH chains are mixed with the mucin. This result further strengthens our hypothesis that the PEG-DA's acrylate end groups can create molecular interaction with mucin glycoproteins.

3.2 Mucoadhesion measurements

The mucoadhesive potential of PEG-DA was evaluated in tensile using fresh small intestine as a model surface. It is well known that all mucosa surfaces share similar total content of glycoprotein and differ in the exact types of these glycoproteins. Since all glycoproteins consist sulfide end groups [3], any mucoadhesion system which is capable of forming covalent bonds with sulfide end groups is likely to form similar bonds with a variety of mucosa surfaces. The results presented below are the maximum detachment force (MDF) required to detach a polymer tablet from the fresh tissue surface.

The mucoadhesion process is believed to be a result of chain penetration, entanglement and molecular interaction (covalent or/and non-covalent). Therefore, it can be described using the diffusion and chemical bonding theories of adhesion. The diffusion theory of adhesion is based on the assumption that the adhesion strength of polymers to themselves (autohesion) or to each other is due to mutual diffusion (inter-diffusion) of macromolecules across the inter-phase. The chemical bonding theory of adhesion invokes the formation of interaction such as covalent, ionic or hydrogen bonds across the adhesive surface inter-phase [30–32].

As can be seen in Fig. 6, increasing the PEG-DA concentration enhances the adhesion to the mucus. This observation could reflect increased chain entanglements which, according to the diffusion theory, is expected to improve the adhesion [30–32]. However, larger polymer concentration also leads to an increase in the concentration of acrylate group near the surface and higher probability of chemical bonds formation. In order to demonstrate the influence of sample preparation conditions and these two possible mechanisms on the adhesion, macromer solutions containing 2 wt% PEG-DA were cross-linked on a hydrophobic surface prior to placing them on the mucus surface and measuring the adhesion strength. As can be seen in Fig. 6, the adhesion strength was significantly lower ($\alpha = 0.05$) compare to the same PEG-DA sample that was cross-linked on the mucosa surface, thus suggesting that by preventing cross-linking on the surface both the diffusion and penetration of PEG-DA chains beneath the surface and the ability to form covalent bonds, were harmed. This result is in a good agreement with previous published work done on the ability of PEG to penetrate and promote adhesion with other polymer surfaces [22–26].

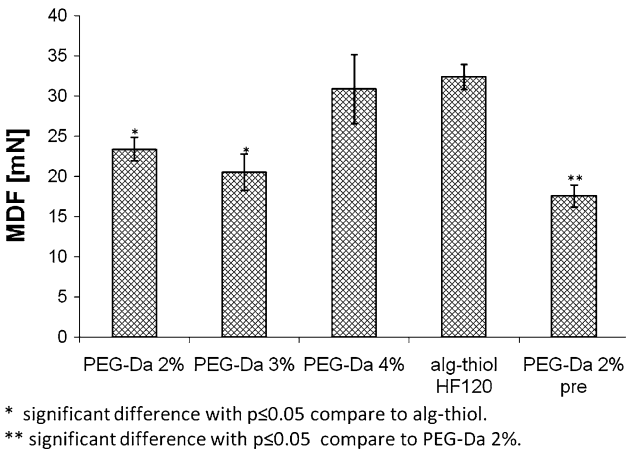

Fig. 6 Maximum detachment force (MDF) for various polymer samples from fresh mucus surface at 25°C

In order to compare the performance of mucoadhesive system based on PEG-DA to known mucoadhesive system based on covalent bonds, we have repeated the experiment with alginate-thiol. Alginate-thiol was synthesized from alginate HF 120RBS (medium G content) as previously described [12]. The maximum detachment force obtained with PEG-DA is of the same order of magnitude as the one obtained with alginate-thiol (Fig. 6). Moreover, we have found a significant difference with the results obtained from the 2 and 3% PEG-DA, whereas the difference between the 4% PEG-DA and the alginate-thiol was not significant.

Previously studied mucoadhesive systems based on thiolated polymers also display comparable adhesion capability. For example, Bernkop-schnurch et al. [33] characterized the adhesion of alginate and alginate-thiol to a commercial-grade crude porcine mucin. Maximum detachment forces of approximately 10 and 70 mN were obtained for alginate and alginate-thiol, respectively. In another study by the same group [6] maximum detachment forces of 27, 256 and 56 mN were measured for low, medium and high molecular weight 2-iminothiolane conjugated chitosan (chitosan-TBA). It should be noted, however, that the exact setup used for the adhesion measurements have a vast influence on the measured force, as described in detail in a recently published review [34]. In particular, the measurements described in the current study were performed using hydrated samples which were cross-linked on the mucus surface, whereas the above mentioned previous studies have utilized dry, compressed sample which did not contain any cross-linker. It is known that during the swelling process of dry sample the polymer chains tend to penetrate to the surface due to their swelling [35, 36]. This process probably leads to an increase in the adhesion ability according to the diffusion theory of adhesion. The new mucoadhesion system presented here displays similar adhesion ability in hydrated environment in spite of the lack of swelling. We believe that characterizing mucoadhesives in their hydrated form is more eligible since it simulates better the hydrated physiology environment existing near mucus surfaces.

3.3 Release studies

Release profiles from PEG-DA matrices were evaluated using a hydrophilic drug as a model. Since several studies describing the ability of PEG to improve Ibuprofen dissolution by creating solid dispersions of PEG with the drug were published, we have chosen Ibuprofen as a model [37–40].

As can be seen in Fig. 7, the kinetics of drug release is rapid, and 100% of the initial dose is released within the first few hours. Ibuprofen is used to treat pain and fever

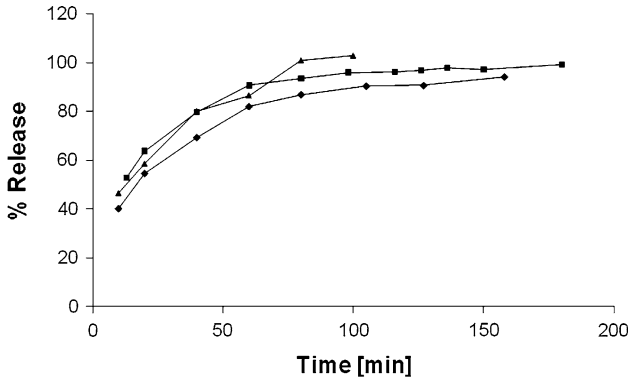

Fig. 7 Ibuprofen release profile from PEG-Da gel tablets having varied polymer concentration (*filled square*) 2% (*filled triangle*) 3% and (*filled diamond*) 4% at room temperature

therefore its relatively rapid release and absorption is essential. Moreover its half life time in the body is around 2 h therefore it should be released in a time range of few hours. Newa et al. [39] have demonstrated shorter release time scale of minutes using a solid dispersions of PEG and Ibuprofen. Drug release from PEG dispersions is expected to be fast due to fast dissolution of the polymer and the large surface area from which the drug diffuses. Therefore, cross-linked PEG-DA matrices offer longer Ibuprofen release time, with the additional benefit of the ability to adhere to mucus.

As expected, the release kinetics can be altered by changing the polymer concentration (Fig. 7). Increasing the polymer concentration has led to slower release kinetics. Such behavior could be attributed to the denser hydrogel network formed at higher polymer concentration [41].

The Ibuprofen release profiles were further analyzed in order to calculate the diffusion coefficients. The analysis was done using the early-time (Eq. 1) and late-time (Eq. 2) approximation equations developed by Ritger and Peppas [42, 43],

$$\frac{M_t}{M_\infty} \cong 4\left(\frac{D_E \cdot t}{\pi \delta^2}\right)^{0.5} \quad (1)$$

$$\frac{M_t}{M_\infty} \cong 1 - \frac{8}{\pi^2} \cdot \exp\left(-\frac{\pi^2 D_L \cdot t}{\delta^2}\right) \quad (2)$$

where M_t/M_∞ is the fractional drug release, t is the release time, D_E and D_L are the early and late diffusion coefficients respectively and δ is the diffusion distance. The diffusion distance δ was set to be half of the tablet width.

As can be seen in Fig. 8 a good fit was obtained using both the late and the early time models. The diffusion coefficients obtained from this analysis are summarized in Table 1. A decrease in the diffusion coefficient is observes when the polymer concentration is increased, due to a decrease in the matrix's mesh size leading to a slower solute diffusion.

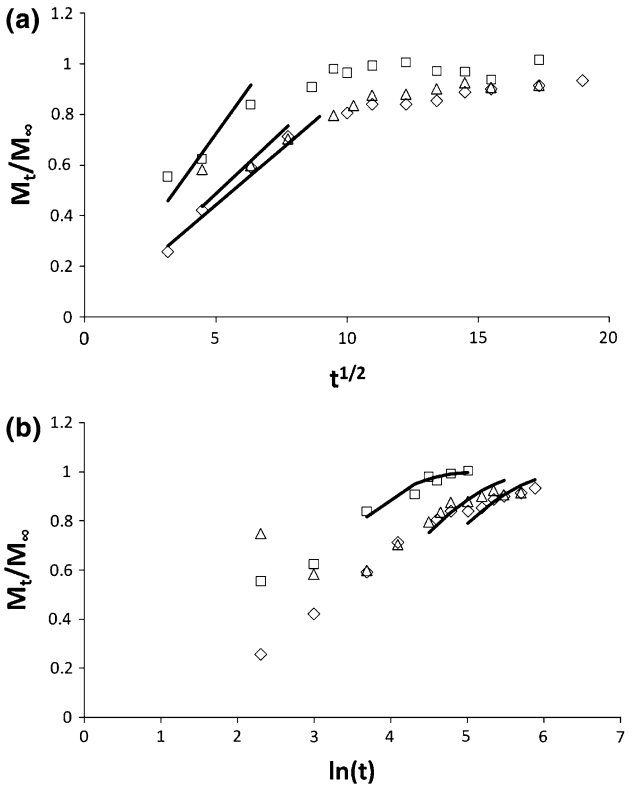

Fig. 8 Fits of the **a** early time model and **b** late time model equations to the release data at polymer concentration of (*open square*) 2% (*open triangle*) 3% and (*open diamond*) 4% at room temperature

Table 1 Diffusion coefficients obtained from the fits presented in Fig. 8

PEG-DA concentration (mg/ml)	D_L (cm^2/s)	D_E (cm^2/s)
20	2.11E-06	1.93E-06
30	9.56E-07	6.83E-07
40	7.85E-07	4.68E-07

The release profiles and the calculated diffusion coefficients suggest that the new mucoadhesive system limits the rate of drug release and thus can act as a drug delivery vehicle. A control of the drug release profile by changing the polymer concentration was demonstrated, yet we believe that further control can be achieved using variation in the molecular weights of PEG-Da as this parameter also affects the mesh size of the network. The combination of both enhanced mucoadhesion properties and controlled drug release abilities opens a way to clinical applications that will benefit from the administration of drugs through the mucosa surface. As an example, administration of drugs with poor bioavailability is more efficient due to the substantially longer retention times. Additionally, drugs which are sensitive to the hostile environment in the GI track can be delivered systemically. Another obvious example is local drug delivery to the surroundings of the mucosa. It should be noted, however, that the cross-linking of the matrix is achieved using an external UV light source and therefore clinical applications are limited to surfaces which are assessable to the operator, such as the oral, nasal or vaginal cavities.

4 Conclusions

A novel mucoadhesive system which can interact covalently with mucin type glycoprotein, and function as a sustained release matrix, was proposed. The ability of PEG-DA to create interactions with mucin type glycoproteins was verified using NMR and rheology experiments. NMR studies have detected disappearance of the PEG-DA's vinyl protons upon mucin addition which can be correlated to vinyl-sulfide interaction. Rheology measurements have shown that mucin addition to PEG-DA has led to viscosity increase, thus providing additional evidence for the formation of mucin-polymer covalent bond.

The ability PEG-DA to attach to mucus and promote mucoadhesion was evaluated in tensile using Lloyed machine. PEG-DA adhered with strength comparable to another covalently interacting mucoadhesive polymers. Furthermore PEG-DA was found to be a suitable candidate for sustained release of the hydrophilic drug Ibuprofen. In addition, the diffusion coefficients were evaluated using the early and late release models and a decrease in their value was detected with respect to polymer concentration.

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