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The importance of gel properties for mucoadhesion measurements: a multivariate data analysis approach

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Abstract

In this study we used tensile strength measurements and a recently developed interpretation procedure to evaluate the mucoadhesive properties of a large set of gel preparations with diverse rheological properties. Multivariate data analysis in the form of principal component analysis (PCA) and partial least square projection to latent structures (PLS) was applied to extract useful information from the rather large quantities of data obtained. PCA showed that the selected series of gels was heterogeneous. Some groupings could be detected but none of the gels was identified as an outlier. By using PLS we investigated the relations between the rheological properties of a gel and the parameters defining the cohesiveness, as measured with the texture analyser used for the mucoadhesion measurements. The rheological properties proved to be important for the results of both the mucoadhesion and the cohesiveness measurements. Furthermore, by using PLS two different measurement configurations were evaluated and it was concluded that the combination of a relatively small volume of gel and two pieces of mucosa seems to be more appropriate than a large volume of gel in combination with one piece of mucosa.

Introduction

Mucoadhesive dosage forms have attracted considerable interest over the years as a means of providing intimate contact and prolonging the residence time at the site of absorption (Peppas & Buri 1985; Gu et al 1988; Dondeti et al 1996; Lee et al 2000). A number of in-vitro methods for measuring the mucoadhesion of solid formulations, such as tablets, compacts and microspheres, have been reported, most of which employ tensile or shear strength measurements (Duchene et al 1988; Peppas & Sahlin 1996). Recently, we presented a tensile strength method suitable for studying the mucoadhesive properties of polymer gels, using freshly excised nasal porcine mucosa and a texture analyser (Hägerström & Edsman 2001).

Several theories have been forwarded to explain the mucoadhesion process (Duchene et al 1988; Gandhi & Robinson 1994; Peppas & Sahlin 1996). For example, the fracture theory of adhesion (Kammer 1983) has been applied to analyse tensile strength measurements on polymer microspheres (Chickering & Mathiowitz 1995) and powder specimens (Bredenberg & Nyström 2003). However, it is likely that different mechanisms are important for solid dosage forms and for fully hydrated systems such as polymer gels (Lehr et al 1992). It is particularly important for gels to consider the possible regions where the failure of the mucoadhesive joint can take place (Smart 1999; Hägerström & Edsman 2001). In a tensile strength measurement, the withdrawal of mucosa from the gel will result in the failure of the weakest of the three regions of the mucoadhesive complex — the gel, the mucus or the interface layer. We have proposed that the cohesiveness of the individual components, the gel and the mucus, should be measured and compared with the results from a mucoadhesion measurement to estimate which region is the weakest (Hägerström & Edsman 2001). In that work we also outlined an interpretation procedure for assessing whether the measured tensile work reflects a cohesive failure of the gel or a genuine interaction of the gel with the mucus layer.

In this study we used tensile strength measurements and the interpretation procedure to evaluate the mucoadhesive properties of a series of 24 gel preparations with

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diverse rheological properties. Several of these gel preparations have, to our knowledge, not been included in any previous mucoadhesion studies.

The employment of multivariate techniques in different pharmaceutical applications is steadily increasing and its usefulness has been reviewed recently (Gabrielsson et al 2002). In the present study we applied multivariate data analysis in the form of principal component analysis (PCA) and partial least square projection to latent structures (PLS) to extract useful information from the rather large quantities of data obtained. More specifically, we investigated the relations between the rheological properties of a gel and the cohesiveness parameters, as measured with the texture analyser. Furthermore, we compared the results obtained using two different measurement configurations and evaluated the three parameters, tensile work, peak force and deformation to failure, that have been put forward as measures of mucoadhesion (Chickering & Mathiowitz 1995; Hägerström & Edsman 2001), with the aim of determining which measurement configuration and which mucoadhesion parameter is the most appropriate.

Materials and Methods

Materials

The polymers used in this study were Carbopol 907, Carbopol 934P and polycarbophil (linear and crosslinked poly(acrylic acid); Noveon Inc., Brecksville, OH), Blanose 7LF and Blanose 7HF (sodium carboxymethylcellulose of low- and high-viscosity grade; Hercules/Aqualon, Alizay, France), linear sodium hyaluronate with molecular weights of 4×10^6 and 5×10^6 (Pharmacia AB, Uppsala, Sweden), linear sodium hyaluronate from *Streptococcus equi* with molecular weight 1.7×10^6 (Fluka, Buchs, Switzerland), Perlane, Restylane and Restylane FineLines (non-animal stabilized hyaluronic acid, NASHA; Q-Med AB, Uppsala, Sweden), Seacure CL 211 (chitosan hydrochloride; Pronova Biomedical, Oslo, Norway), Pluronic F-127 (polyoxyethylene:polyoxypropylene block copolymer; BASF Corp., Parsippany, NJ) and Kelcogel F (deacetylated gellan gum; Kelco division of the Monsanto company, Tadworth, UK). All polymers were the kind gifts of the manufacturers. All other chemicals were purchased from Sigma (St Louis, MO) and were of analytical or ultra quality. Ultra-pure water was used throughout the experiments. Fresh porcine nasal mucosa from Pigham pigs was obtained from the local slaughterhouse (Swedish Meats AB, Uppsala, Sweden).

Gel preparation

A summary of the polymers and concentrations used is provided in Table 1. Poly(acrylic acid) samples were prepared by dispersing the required amount of polymer in 0.9% NaCl. The pH was adjusted to approximately 6.5–7 using 4.5 M NaOH and the samples were equilibrated at 4 °C. The following day, the pH was finely adjusted to 7.4 and 0.9% NaCl was added to obtain the polymer concentration required. Sodium carboxymethylcellulose samples and linear sodium hyaluronate (MW 1.7×10^6) samples were prepared by stirring the required amount of polymer and 0.9% NaCl until completely dissolved (about 15–20 h). The chitosan samples were prepared in the same way, then the pH was adjusted to approximately 6.5. Sodium hyaluronate samples with higher molecular weights were obtained from the manufacturer as solutions (Healon samples), then diluted to exact concentration using a physiological phosphate buffer, pH 7.0–7.5 (Pharmacia Corp., Uppsala, Sweden). Careful mixing was carried out to ensure that the samples were homogeneous. The NASHA samples (Perlane, Restylane and Restylane FineLines) were obtained from the manufacturer as gels and were used as received. Pluronic F-127 samples are known to undergo thermoreversible gel formation at the concentrations used, so the samples were prepared by stirring the required amount of polymer and 0.9% NaCl at 4 °C until complete dissolution had taken place. The samples were then allowed to equilibrate at room temperature to form a clear gel. Gellan gum samples were prepared by stirring the required amount of polymer and 0.9% NaCl in a sealed vial at 100 °C for 20 min, using a water-bath placed on a magnetic heater/stirrer. After cooling at room temperature the samples were sieved using a 0.5-mm standard set of sieves, to obtain a particulate gel.

Table 1 Summary of the gel preparations.

Gel preparation no.	Polymer	Concn (% w/w)
1, 2	Linear poly(acrylic acid) (Carbopol 907)	2.0, 7.4
3, 4	Cross-linked poly(acrylic acid) (Carbopol 934)	0.75, 2.0
5, 6	Cross-linked poly(acrylic acid) (Polycarbophil)	0.75, 2.0
7	Low viscosity NaCMC (Blanose 7LF)	7.4
8	High viscosity NaCMC (Blanose 7HF)	2.0
9–12	Linear SH, MW 4×10^6	0.5, 1.0, 1.5, 2.0
13, 14	Linear SH, MW 5×10^6	0.5, 1.0
15	Linear SH, MW 1.7×10^6	2.0
16	NASHA (Perlane)	2.0
17	NASHA (Restylane)	2.0
18	NASHA (Restylane FineLines)	2.0
19, 20	Chitosan (Seacure CL 211)	2.0, 7.0
21, 22	Poloxamer (Pluronic F-127)	20.0, 25.0
23, 24	Gellan gum (Kelcogel F), 0.5 mm mesh sieve	0.25, 0.5

NaCMC, sodium carboxymethylcellulose; SH, sodium hyaluronate; NASHA, non-animal stabilized hyaluronic acid.

Rheological characterisation

Rheological measurements were carried out at 37 °C to characterise the preparations using a Bohlin VOR

rheometer (Bohlin Reologi, Lund, Sweden), a controlled rate instrument of the couette type. The measuring system used was a concentric cylinder (C14). Upon loading in the measuring geometry, the samples were lightly centrifuged for 1 min at 209 *g* to remove entrapped air. The surface of the sample was then covered with silicon oil to avoid dehydration during measurement, and the sample was allowed to equilibrate for 30 min. The first measurement conducted was a strain sweep made at a constant frequency of 1 Hz to determine the linear viscoelastic region for each of the samples. From this, a strain amplitude was selected, within the linear region of the sample (i.e., below the maximum strain amplitude), then a frequency sweep (0.01–5 Hz) was performed. From the frequency sweep, the elastic (storage) modulus (G'), the viscous (loss) modulus (G''), and the phase angle (δ) were determined. These rheological parameters, obtained at the frequencies 0.05 and 1 Hz, were used as the input matrix in the principal component analysis, which was performed to investigate the rheological diversity of the samples.

Tissue preparation

The time that elapsed from the slaughter of the pig to the removal of the snout was approximately 2 min. After making a longitudinal incision through the septum wall and exposing the nasal cavity on each side of the septum, the cavity mucosa (i.e., the mucous membrane covering the turbinates) was carefully removed as previously described (Hägerström & Edsman 2001). Small circular pieces of mucosa (diameter 14 mm) and larger rectangular ones (approximately 2×3 cm) were cut out from the central parts of each cavity mucosa. The pieces obtained were then kept in ice-cold TRIS buffered sucrose solution (Tobyn et al 1995) until use, a maximum delay of 5 h.

Tensile strength measurements

A texture analyser, TA.HDi (Stable Micro Systems, Haslemere, UK), equipped with a 5 kg load cell, was used for all tensile strength measurements. Two slightly different configurations were used. In the configuration using a large volume (Figure 1A), the gel was placed in a cylindrical container, holding approximately 70 mL of gel. One circular piece of mucosa was used; this was attached to the upper movable probe as described elsewhere (Hägerström & Edsman 2001). In the configuration using a small volume (Figure 1B), on the other hand, two pieces of mucosa were used. A circular piece was attached to the upper probe and a larger rectangular piece was attached to the lower, stationary part of the instrument. Gel (100 μL) was placed onto the lower mucosa, whereupon the upper mucosa was lowered until contact was made with the gel. In both of the configurations, the gel and the mucosa were kept in contact for 2 min, and then the upper mucosa was withdrawn upwards at a speed of 0.1 mm s^{-1} until detachment occurred. During the entire measurement a force–distance curve was recorded, from which the tensile work (i.e., the area under the curve during the withdrawal phase), the peak force and the deformation to failure were determined using the computer software Texture Expert Exceed (Stable Microsystems, Haslemere, UK). These parameters were defined according to Figure 2, and were used as measures of the mucoadhesion as suggested elsewhere (Chickering & Mathiowitz 1995; Hägerström & Edsman 2001).

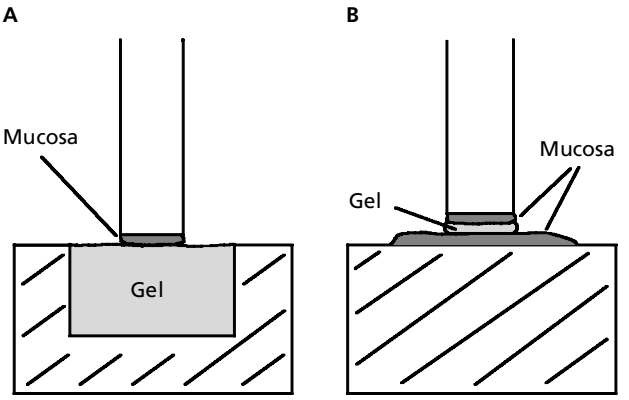

Figure 1 Experimental configurations used in the mucoadhesion measurements. A. Large volume configuration. B. Small volume configuration.

The cohesiveness of the gels was investigated by lowering and withdrawing the stainless-steel probe alone against the gel (i.e., without mucosa), with the same experimental settings as used in the mucoadhesion measurements. The failure was found to be within the gel for all preparations studied, as a small amount of gel always remained on the surface of the probe after the measurement.

The cohesiveness of the mucus was used to assist with the interpretation of the mucoadhesion measurements, and was taken from Hägerström & Edsman (2001).

Interpretation of mucoadhesion data

The interpretation procedure used here was adopted from Hägerström & Edsman (2001), and offers a good basis from which to assess whether the measured tensile work reflects a

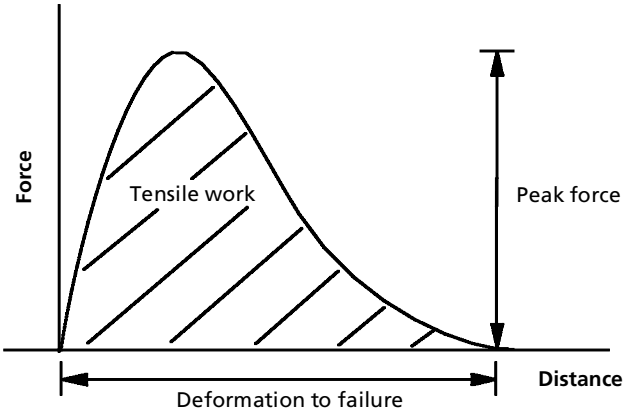

Figure 2 Force–distance curve defining the tensile work, the peak force and the deformation to failure.

cohesive failure of the gel or a genuine interaction of the gel preparation with the mucus layer. Briefly, this involves measuring the cohesiveness of the gel and the mucus layer independently, and comparing the values obtained with the result of a mucoadhesion measurement. If the value for the mucoadhesion work is higher than that of the cohesive work of the mucus, strengthening of the mucus layer must have occurred during the contact with the gel. Furthermore, if the mucoadhesion work is also lower than the cohesive work obtained for the gel, it can be deduced that the mucoadhesion measurement reflects the strengthened mucus layer and not the cohesive failure of the gel.

In the Results section, the abbreviations TW, PF and DF are used to denote the tensile work, the peak force and the deformation to failure, respectively. The subscript mucoad indicates the result of a mucoadhesion measurement, whereas the subscripts gel and muc indicate the results of measurements of the cohesiveness of the gel and the mucus layer, respectively.

Data analysis

The rheological diversity of the chosen series of gels was analysed with principal component analysis (PCA) (Simca-P v. 8.0; Jackson 1991). PCA summarizes the variation in the X-space, gives an overview of the data, and reveals groups of observations, trends and outliers (Jackson 1991).

The mucoadhesion data were analysed statistically by using one-way analysis of variance and, subsequently, Dunnett's multiple comparison test, when comparing multiple groups, and an unpaired, two-tailed *t*-test when comparing two groups. The significance level (α) was set to 0.05.

In addition, the mucoadhesion measurements and the measurements of the cohesiveness of the gels were evaluated by partial least square projection to latent structures (PLS) (Simca-P v. 8.0; Höskuldsson 1988). This multivariate method takes PCA a step further as it deals with both descriptive (X) and response (Y) data. PLS is used for prediction of response parameters and relates two data matrices to each other by a linear multivariate model using latent structures (Höskuldsson 1988; Gabrielsson et al 2002). For the interested reader, a more theoretical description of PLS can be found in, for example, Geladi & Kowalski (1986).

Skewed variables were transformed using the cubic root or logarithm before the multivariate analysis. Variables that did not obtain a value for the skewness within −1.5 to 1.5 were excluded to avoid them obtaining too heavy a weighting in the data analysis. The numbers of PLS components computed were assessed by Q^2, the leave-one-out cross-validated R^2, using seven cross validation rounds. Only PLS components resulting in a positive Q^2 were computed. The models were refined through stepwise selection of the variables. If the exclusion of the least important variable resulted in a more predictive model (as assessed by a higher Q^2), then that descriptor was permanently left out of the model. The variable selection procedure was repeated until no further improvement of the model was achieved.

Results and Discussion

PCA analysis of the rheological diversity

We wanted to ensure that a heterogeneous set of gels was used in the mucoadhesion measurements to enable conclusions to be drawn that would be valid for gels with a variety of consistencies. Therefore, we analysed the rheological diversity of the selected series of gels with PCA. Three principal components were extracted in the analysis, the first two of which explained 98% of the rheological diversity (Figure 3). The dataset covered all four quadrants of the PCA plot, showing that the selected series of gels was heterogeneous. Furthermore, none of the gels was identified as an outlier. Some groupings could be detected, as expected. Preparations 9–12, which were based on the same polymer but with different concentrations, were distributed in a linear manner. Preparations 3 and 5, 4 and 6, and 21 and 22, respectively, were similar in terms of the nature of the polymer and the concentration and, not surprisingly, the two halves of each pair were located in close proximity to each other. Furthermore, the fluid-like preparations (1, 2, 7, 19) were located furthest to the left. A somewhat unexpected grouping of data was also found in the score plot: particulate gels with high values of G′ (4, 6, 16, 17, 23, 24) were located in a cluster in the lower right quadrant.

Interpretation of mucoadhesion measurements

In Figure 4 the mucoadhesion parameters and the cohesiveness parameters of the gel and the mucus are shown, for both the large and the small volume configuration. In the

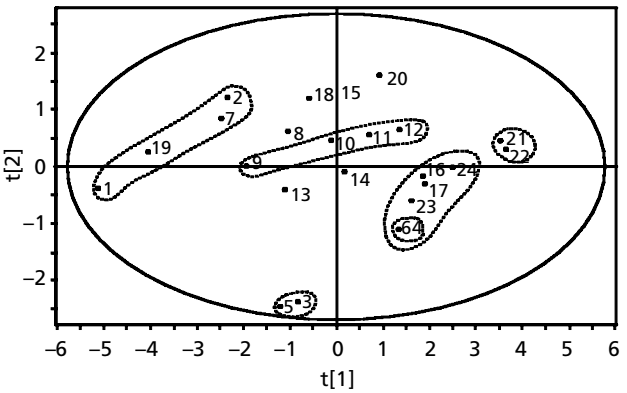

Figure 3 Rheological heterogeneity of the selected gels investigated by principal component analysis (PCA). The scores of the first two principal components (t1 and t2) describing 98% of the diversity of the descriptor space are shown. The elastic modulus, the viscous modulus and the phase angle, each of which was obtained at the frequencies 0.05 Hz and 1 Hz, were used as the input matrix. The dataset covered all four quadrants of the PCA plot, showing that the selected series of gels was heterogeneous with respect to the rheological properties. None of the gels in the selected series were identified as outliers. The gels are indicated by numbers, referring to those listed in Table 1. Groupings are indicated by dotted lines.

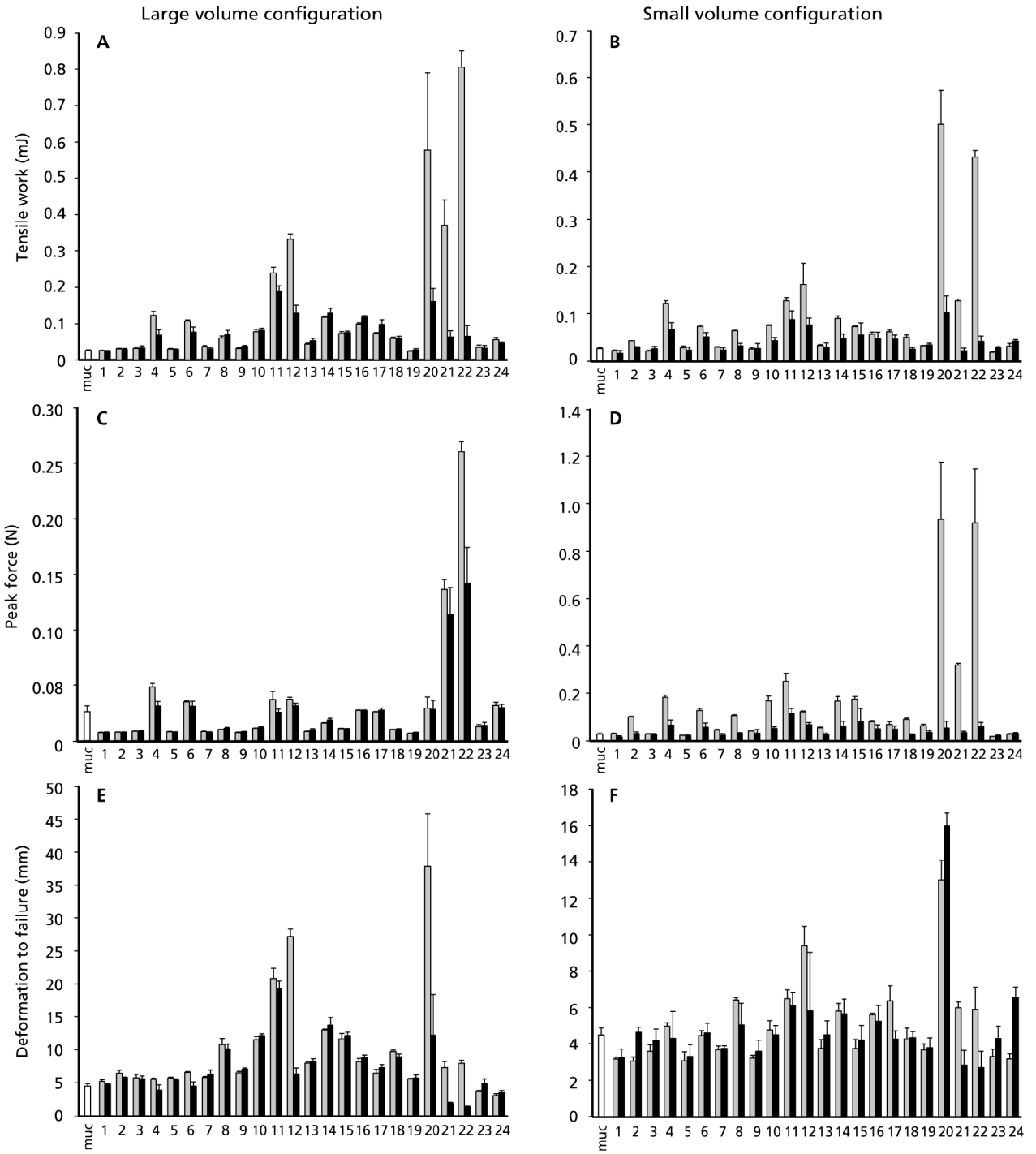

Figure 4 Plots of the measurements made for the interpretation of mucoadhesive properties of the gel preparations. The tensile work (A, B), the peak force (C, D) and the deformation to failure (E, F) obtained from mucoadhesion measurements (black, n = 3–12) and from measurements of the cohesiveness of the gel preparations (grey, n = 3–12) and the mucus layer (white, n = 25). Data from the large volume configuration are shown in panels A, C and E, and data from the small volume configuration in panels B, D and F.

following, the results for the tensile work will be interpreted. Of course, corresponding reasoning can also be conducted for the peak force and the deformation to failure. From the results for the tensile work shown in Figure 4A, B, it can be seen that for some gel preparations (e.g., 1, 3, 5, 7 and 19), the mucoadhesion work (TW_{mucoad}) did not differ significantly from either the cohesive work of the gel (TW_{gel}) and the mucus (TW_{muc}). For other gels (e.g., 15 and 16), the TW_{gel}

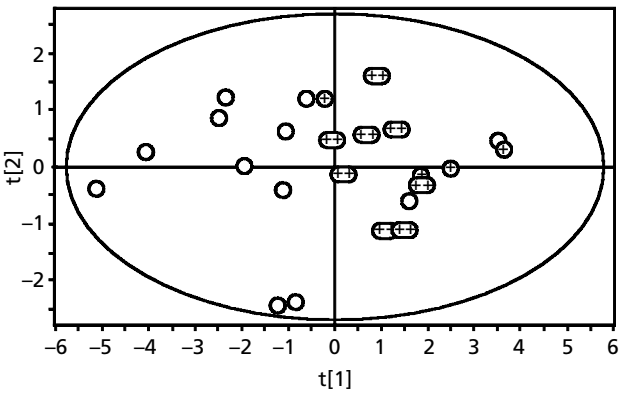

Figure 5 The PCA score plot showing the mucoadhesive properties of the gel preparations as interpreted from measurements using the small volume configuration. The gels are assigned different symbols according to whether they strengthened the mucus or not: ○, gels that provided no strengthening; ⊕, gels that improved the strength; ⊖, gels that strengthened the mucus and in which the failure occurred in the strengthened layer.

and the TW_{mucoad} were approximately the same, but significantly higher than the TW_{muc}, implying that a strengthening of the mucus layer had taken place. Furthermore, for e.g. gels 4, 6, 11 and 12, 20 and 22, the TW_{mucoad} was not only higher than the TW_{muc}, it was also lower than the TW_{gel}, indicating that a strengthening of the mucus had taken place, and that the mucoadhesion measurement reflected the strength of the mucus and not the cohesive properties of the gel. In the PCA score plot these gels were located in the right half, whereas the ones giving no strengthening of the mucus were located in the left half (Figure 5). In this respect, the results were consistent irrespective of the configuration used. The gels giving rise to strengthening of the mucus included linear and cross-linked gel preparations, characterised by having substantially higher values of G′ and G″ compared with the weaker preparations that did not give any strengthening of the mucus.

PLS analysis of the cohesiveness data

Previously we speculated that the parameters obtained from a mucoadhesion measurement could reflect certain rheological properties of a gel (Hägerström & Edsman 2001). For example, we observed that cross-linked gels with pronounced elastic properties exhibited high peak forces, whereas linear low-concentration preparations with a pronounced viscous character showed a considerable amount of deformation. Similar observations were made in this study and hence we decided to use PLS analysis to investigate the relation between the rheological properties and the cohesiveness parameters. The better the cohesiveness parameters can be predicted by the rheological properties, the stronger the relation. In Table 2 the PLS models for the cohesiveness parameters are shown. Several conclusions could be drawn from these data, irrespective of the configuration used. For the peak force of the gel (PF_{gel}) fairly good models were obtained ($R^2 = 0.75$ and 0.56, respectively, for the large volume and small volume configuration), in which the most important rheological descriptor was the elastic modulus (G′). The deformation parameter (DF_{gel}), on the other hand, was principally described by the viscous modulus (G″), even though the models did not have a high predictive power ($R^2 = 0.38$ and 0.39, respectively). The cohesive work of the gel (TW_{gel}) is a bit more complex and was best described by several different rheological descriptors, resulting in models with a predictive power almost as high as for the PF_{gel} ($R^2 = 0.65$ and 0.55, respectively). Since the TW_{gel} is obtained from the area under the force–distance curve, and thus incorporates both the peak force and the deformation to failure, it was not unexpected that several rheological descriptors were needed.

PLS analysis of the mucoadhesion data

In the next step, we performed PLS analysis of the mucoadhesion parameters, using the rheological and the cohesiveness parameters as the input (X variables) matrix, with the intention of identifying important descriptors and comparing the two measurement configurations. The PLS analysis was performed in two steps: in the first step, only the rheological parameters were included in the input matrix; then a corresponding analysis was made but with both the rheological and the cohesiveness parameters being used as variables, and whether or not the model was improved by including the cohesiveness data was investigated.

Table 2 PLS models for the gel cohesiveness parameters.

	Large volume configuration			**Small volume configuration**		
	TW_{gel}	PF_{gel}	DF_{gel}	TW_{gel}	PF_{gel}	DF_{gel}
R^2	0.65	0.75	0.38	0.55	0.56	0.39
Q^2	0.60	0.73	0.26	0.49	0.53	0.33
Rheological descriptors[a]	all	log G′ (1 Hz) log G′ (0.05 Hz)	log G″ (0.05 Hz) δ (0.05 Hz) log G′ (1 Hz)	log G″ (0.05 Hz) δ (0.05 Hz) log G′ (0.05 Hz)	δ (0.05 Hz) log G′ (1 Hz) log G′ (0.05 Hz)	log G″ (0.05 Hz) log G″ (1 Hz)

[a]The descriptors are given in order of importance.

To analyse which one of the two measurement configurations was the most appropriate, a rather unconventional interpretation of the models was made: here, we did not seek to attain models with an extremely high predictive power. The reason for this was that if the gel properties were found to be excellent predictors of the mucoadhesion property used as the response (Y variable) parameter, i.e., if models with a high predictive power (high R^2 and Q^2) were obtained from the gel properties alone, this would mean that the mucoadhesion measurement solely reflected the properties of the gel preparation. Moreover, this would indicate that the presence of a piece of mucosa in the measurement configuration would make no difference to the results obtained, that is, the mucosa was irrelevant to the measurement because the gel properties determined the result. In such a case, the configuration cannot be considered to be optimal for studying possible mucoadhesive effects. On the other hand, one should expect the gel properties to have at least some capacity to predict the mucoadhesive interactions. This is because the rheological properties of the gel are related to physicochemical factors such as the molecular weight, cross-linking density and molecular flexibility, which are features that are generally considered to be important for the formation of entanglements during the mucoadhesion process (Gu et al 1988; Leung & Robinson 1990; Junginger 1991).

The results from the stepwise PLS analysis of large and small volume data are presented in Table 3. Unfortunately, the deformation parameter could not be modelled since the transformation failed to obtain a normal distribution of this response parameter. Consequently, in the following, only the peak force and the tensile work are discussed.

For the large volume configuration, the PLS model for PF_{mucoad}, obtained when using only rheological data as the input matrix, was similar to that for PF_{gel} (compare Tables 2 and 3). It was found that in both models the predictive power was high and the G′ data were the most important descriptors in both of the models. If the cohesiveness parameters were included in the input matrix, the PF_{gel} was also found to contribute to the model for PF_{mucoad}, and the predictive power was increased markedly ($R^2 = 0.98$). From these results it can be deduced that, with this configuration, the PF_{mucoad} mainly reflected the gel properties (mostly PF_{gel}), and thus the gel properties would have a considerable impact on the mucoadhesion measurement. This could also be anticipated from Figure 4C, where, for most of the gel preparations, very little difference was observed between the PF_{gel} and the PF_{mucoad}. For the small volume configuration, on the other hand, the models for PF_{gel} and PF_{mucoad} had lower predictive power and different descriptors were important. G′ was an important descriptor for PF_{gel}, whereas G″ and the cohesiveness parameters were necessary to describe PF_{mucoad}. In contrast to the large volume configuration, here the mucoadhesion measurement did not solely reflect the properties of the gel preparation since other information than that included in the input matrix was found to be necessary to describe the PF_{mucoad}. Consequently, the small volume configuration seems to be a better approach for the mucoadhesion measurements than the large volume configuration.

Furthermore, it can be argued that, because the peak force could reflect the gel properties to a larger or smaller extent depending on the measurement configuration, the use of the peak force as the sole mucoadhesion parameter could be associated with unreliability when comparing results between studies with different measurement settings.

The interpretation of the results from the PLS analysis of the tensile work was not as straightforward as it was for

Table 3 PLS models for the mucoadhesion parameters.

	Large volume configuration			**Small volume configuration**		
	TW_{mucoad}	PF_{mucoad}	DF_{mucoad}	TW_{mucoad}	PF_{mucoad}	DF_{mucoad}[c]
R^{2a}	0.40[a]	0.79[a]	n.s.[a]	0.25[a]	0.24[a]	
Q^{2a}	0.33[a]	0.78[a]	n.s.[a]	0.18[a]	0.21[a]	
Rheological descriptors[a]	log G′ (1 Hz) log G″ (0.05 Hz) log G″ (1 Hz)	log G′ (1 Hz) log G′ (0.05 Hz)	n.s.	log G″ (0.05 Hz) log G″ (1 Hz)	log G″ (0.05 Hz) log G″ (1 Hz)	
R^{2b}	0.74[b]	0.98[b]	0.64[b]	0.59[b]	0.44[b]	
Q^{2b}	0.71[b]	0.96[b]	0.48[b]	0.53[b]	0.38[b]	
Rheological and cohesiveness descriptors[b]	log DF gel log G″ (0.05 Hz)	log PF gel log G′ (1 Hz) log TW gel	log DF gel log PF gel δ (0.05 Hz) δ (1 Hz) log G′ (0.05 Hz) log G′ (1 Hz)	log TW gel log DF gel	log G″ (0.05 Hz) log PF gel log TW gel	

[a]Only the rheological parameters were used as the input (X) matrix. The descriptors are given in order of importance. [b]The rheological descriptors and the cohesiveness parameters were used as the input (X) matrix. The descriptors are given in order of importance. [c]Skewed data, could not be modelled.

the peak force. The tensile work models did not have as high a predictive power as had the peak force models and, in addition, there were different descriptors included in the models for TW_{mucoad} and TW_{gel} (compare Tables 2 and 3). For both of the configurations, the models improved when including the cohesiveness parameters in the input matrix, although the highest predictive power was obtained for the large volume configuration ($R^2 = 0.74$). Similarly, as concluded from the peak force analysis, it seemed that the small volume configuration was a better choice for the mucoadhesion measurements, even though the difference was not as apparent as it was for the peak force.

In previous studies the tensile work has been put forward as a more suitable mucoadhesion parameter than the peak force (Duchene & Ponchel 1989; Hägerström & Edsman 2001). For the large volume configuration this seems to be a valid claim, since, in this study, the gel properties did not have such a significant impact on the tensile work as they had on the peak force. However, the same observation cannot be made from the models obtained with the small volume configuration. Thus, a general conclusion concerning which mucoadhesion parameter is the most appropriate cannot be drawn from the work presented here, since it is largely dependent on the way the measurements are conducted.

Conclusions

In this work we have presented mucoadhesion data for a large set of gel preparations with diverse rheological properties and we have proved the more general applicability of the interpretation method that we proposed in recent work (Hägerström & Edsman 2001).

The usefulness of multivariate data analysis for evaluating experimental results and extracting information from large quantities of data has been demonstrated. By using PLS we have evaluated two different measurement configurations in a unique way and concluded that a configuration with a relatively small volume of gel and two pieces of mucosa seems to be more appropriate than a large volume of gel in combination with one piece of mucosa for the determination of mucoadhesion.

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