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European Journal of Pharmaceutics and Biopharmaceutics 52 (2001) 121–127

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

In vitro assessment of the mucoadhesion of cholestyramine to porcine and human gastric mucosa

Sarah J. Jackson[a,*], Alan C. Perkins[b]

[a]*Department of Surgery, University Hospital, Queen's Medical Centre, Nottingham, UK*
[b]*Department of Medical Physics, University Hospital, Queen's Medical Centre, Nottingham, UK*

Received 27 November 2000; accepted in revised form 20 April 2001

Abstract

Previous in vivo studies have suggested that the extended gastric residence and uniform intragastric distribution of cholestyramine may be due to mucoadherent properties. This series of in vitro investigations explored the possibility of the anion exchange resin exhibiting bioadhesive behaviour, and investigated the characteristics, such as particle size and surface charge, that may affect it. Tensile strength measurements were carried out to determine the mucoadhesion of cholestyramine and other test materials (resin particulates, polymers and hydrogels) with varying adhesive properties, to isolated porcine and human gastric mucosa. Optimal instrumental parameters for the system were determined initially and used; all procedures were carried out at room temperature (22°C). The particle size of cholestyramine did not affect mucoadhesion to either porcine or human gastric mucosa ($P = 0.673$, porcine; $P = 0.969$, human), whilst anionic exchangers were found to provide better mucoadhesion than cationic exchangers ($P = 0.0002$, porcine; $P = 0.0009$, human). In some instances, it was found that the detachment forces recorded were lower with human gastric mucosa than with porcine gastric mucosa, although this was not consistently statistically significant. A rank order of mucoadhesion was constructed from a comparison of cholestyramine with eight other test materials. Cholestyramine produced the second highest degree of mucoadhesion, with Carbopol producing the greatest adhesion. Dextran and polyethylene glycol did not display good mucoadhesion under these conditions. From the findings presented here, we have found that cholestyramine demonstrates good mucoadhesion to both porcine and human gastric mucosa when compared to other known bioadhesives. It is suggested that particle size does not contribute to this mucoadherent behaviour but the surface charge of the resin has a significant part to play.

Keywords: Mucoadhesion; Cholestyramine; Gastric mucosa; Ion exchange resin; Porcine; Human; Anionic exchanger; Cationic exchanger; Bioadhesive; Rank order; Particle size

1. Introduction

Previous studies have shown that cholestyramine, an anion exchange resin, exhibits prolonged gastric residence, with between 20 and 30% still remaining at 5.5–6 h, and evenly coats the stomach wall [1,2]. The properties of this resin, when investigated in healthy volunteers using gamma scintigraphy, were found to be largely independent of dose volume, resin particle size or the subsequent feeding of subjects, and suggested a mucoadherent behaviour [1,2]. Ion exchange resins have also proved useful as drug carriers, releasing the drug from the resinate following an influx of competing ions [3,4]. With the increased interest in bioadhesive drug delivery systems, the combination of mucoadherent properties and drug release characteristics could be of value as a potential mucoadhesive drug delivery system to the stomach.

A common method for assessing the in vitro mucoadhesion of a particular test substance is the measurement of peak detachment force; the force required to separate a potential bioadhesive from mucus or mucosa. There are three types of measurements; tensile testing, in which the stress is applied evenly and perpendicular to the adhesive joint, shear testing in which the stress is applied parallel to the joint, and peel which limits the stress to a fine line at the edge of the joint. Tensile strength measurements, although in this instance do not replicate the physiological environment of the stomach or the forces encountered, can be used to investigate factors affecting bioadhesion, and provide comparisons between a potential bioadhesive and known bioadhesives. As methods and instruments vary and as each test substance may perform differently under varying

* Corresponding author. Human Nutrition Research, Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, CB1 9NL, UK.
Tel.: +44-1223-426356; fax: +44-1223-437515.
E-mail address: sarah.jackson@mrc-hnr.cam.ac.uk (S.J. Jackson).

0939-6411/01/$ - see front matter
PII: S0939-6411(01)00156-4

conditions, it is generally accepted that the optimum parameters should be established for each substance prior to testing. Many different animal models have been used in these tensile strength measurements, such as purified porcine mucus extracts [5,6] and isolated tissue from rabbit [7,8], rat [6,9] and pig [10], but to the authors' knowledge there has been no in vitro assessment of mucoadhesion using human gastric mucosal tissue. Recent studies by the author have shown that cholestyramine has the characteristics of a mucoadhesive when in contact with isolated gastric mucosa. However, although it was possible to obtain mucoadhesion to thawed frozen human gastric mucosa in a similar manner to animal tissue, the degree of adhesion was reduced [11].

It had been previously suggested that the extended gastric residence of the cholestyramine seen in vivo was due to entrapment of the small resin particles in the folds of the stomach [1]. It was also thought that as no significant difference was found in the extended gastric residence when the resin was polymer-coated, resin particle size might play a contributory role [2]. The particle size could also relate to the surface area available for bioadhesion, while an increase in the mesh size of polymers could increase the mobility of the polymeric chains and hence aid mucoadhesion [12]. One study did however disagree with the role of particle size in prolonged gastric residence and suggested that some factor other than particle size per se was responsible [13].

It is known that surface charge affects bioadhesion, with anionic polymers exhibiting greater bioadhesion than cationic polymers [14,15], possibly due to hydrogen bonding. Thairs et al. however found no significant difference in the extended gastric residence of cholestyramine and the polymer-coated cholestyramine in vivo and concluded that surface charge was therefore not a necessity for the apparent mucoadhesion [2].

Once optimal values for the experimental parameters had been established, the aims of the present study were to assess whether cholestyramine would exhibit mucoadhesion under in vitro conditions and whether this could be related to the effects seen in vivo. The effects of particle size and surface charge on the apparent mucoadhesion of ion exchange resins, with particular reference to cholestyramine, to both porcine and human gastric mucosa were also assessed. The mucoadhesion of cholestyramine was also compared to that of other known bioadhesives and additional test materials with very little adhesion capabilities.

2. Materials and methods

2.1. Materials

All ion exchange resins were regenerated according to the manufacturers' instructions. The anionic exchangers, cholestyramine (Duolite® AP-143, Rohm and Haas, France SA) and Amberlite® CG-400 (Fluka Chemicals, Dorset, UK) were regenerated using alternate washings in 1.5 M NaOH and 2 M HCl with a final soak in 1.5 M NaOH. The cationic exchange resins, Amberlites® IRP-69 (Sigma Chemical Co., Dorset, UK), CG-50 (Sigma Chemical Co., Dorset, UK) and IR-120 (BDH Ltd., Poole, UK) were regenerated using alternate washings in 2 M HCl and 1.5 M NaOH with a final soak in 2 M HCl. The resins were then rinsed and dried thoroughly. This method of regeneration is well documented [3,4] and had been used previously to regenerate cholestyramine [11]. 2 M hydrochloric acid (HCl) was obtained from Fisher Scientific (Loughborough, UK) and used as supplied. Sodium hydroxide (NaOH) pellets, obtained from BDH Ltd. (Poole, UK), were used to make up 1.5 M NaOH. Other test materials used were sodium alginate and tragacanth obtained from BDH Ltd, Poole UK, polyethylene glycol (PEG) and hydroxypropylmethylcellulose (HPMC) from Aldrich Chemical Co., Dorset UK, dextran and sephadex from Sigma Chemical Co., Dorset UK, sucralfate powder from Wyeth Manufacturing, UK, and Carbopol 974 PNF from BF Goodrich, UK. These test materials were used as supplied, with no additional preparation.

The powdered test materials were used to coat a round glass disc (diameter = 22 mm, surface area = 380 mm^2) using cyanoacrylate glue (Bostik Superglue 4). The powder formed a layer of the test material on the disc which provided a means of attachment to the probe of the tensiometer.

2.2. Equipment

A modified tensiometer was used for the measurement of peak detachment forces, similar to that described in previous studies [9,10,16], and is detailed elsewhere [11]. A probe was suspended from the balance, to which the disc holding the test material was attached, and the arm was then levelled in order to start the experiment from a zero force position. The balance was calibrated at the start of each experiment.

2.3. Methods

2.3.1. Preparation of porcine gastric mucosal tissue samples

Fresh porcine stomachs were obtained from a local abattoir. The tissue was handled carefully to prevent disruption of the mucus layer, and prepared within 2 h of the death of the animal. Tobyn had previously found that there was no significant decrease in the quality of the mucus within this time [17]. The mucosa was carefully separated from the underlying tissue and dissected into samples. The samples were snap-frozen in liquid nitrogen and kept at −80°C. When required, the samples were thawed at 2–4°C overnight and gradually brought to room temperature. Samples taken from the body of the stomach were used, as previous studies found that lower forces of detachment were obtained with the fundal and antral portions of the stomach; the

fundal region having less mucus available for mucoadhesion and the antral portion having greater amounts of mucus resulting in rupture within the mucus layer itself rather than between the test material and the mucus [11].

2.3.2. Preparation of human gastric tissue samples

Human gastric mucosa was obtained through the Department of Surgery, Queen's Medical Centre, from excess tissue removed during surgical procedures in cases of gastric cancer. Healthy portions of human gastric tissue were used; these were identified on the basis of the appearance of normal gastric mucosa. Again, the tissue samples were taken from the body of the stomach and were snap-frozen and thawed when required. Previous studies have shown that although there was a slight reduction in the forces of detachment to thawed frozen tissue when compared to freshly excised tissue, this was not statistically significant [11].

2.3.3. Peak detachment force measurements

The tissue sample, having been thawed and brought to room temperature, was attached to a clean glass plate with cyanoacrylate glue, mucosal side uppermost, and was secured to the base of the tensiometer. The sample was raised to meet the disc attached to the probe. Once in contact, a loading weight of 2.5 g was applied and left in contact with the sample for 10 min. This ensured constant even contact between the probe and the tissue. The weight was removed and the experiment started. The probe was raised at a constant rate of 5 mm/s. The optimal instrumental parameters for mucoadhesion within this system were determined by altering the separation rates (ranging from 0.5 to 5 mm/s), the contact times (0, 2, 7, 10, 20 and 30 min) and the loading or applied forces (0–5 g). A new sample of thawed frozen gastric mucosal tissue and a fresh disc containing the test material was used for each measurement. The procedure took place in an air-conditioned room where the temperature was kept constant at 22°C. This was repeated for both porcine and human gastric mucosa.

Once the optimal experimental values had been determined for both porcine and human gastric mucosa, the effects of cholestyramine particle size and the surface charge of ion exchange resins on the potential mucoadhesion were evaluated. Particle size fractions of cholestyramine were milled using a rotating ball-mill, and sieved through a series of standard sieves into three separate bands, <40 μm, 40–90 μm and 90–125 μm. A sample from each of the sieved fractions was then analysed using a Malvern Mastersizer (Malvern Instruments Ltd., Worcs. England) in the Department of Pharmaceutical Sciences to confirm the particle size range. The potential mucoadhesion of cholestyramine was compared to other ion exchange resins to determine the effect of surface charge. One additional anionic exchanger, Amberlite® CG-400, and three cationic exchangers, Amberlites® IRP-69, CG-50 and IR-120, were tested. These resins had been previously milled and were of a similar particle size range (between 50–150 μm) to cholestyramine that no further milling was necessary. A second series of investigations was carried out in order to compare cholestyramine to other test materials with varying adhesive properties and strengths. Each test material was used as supplied with no additional preparation.

Scanning electron micrographs (SEM) were also taken of the milled cholestyramine resin in contact with porcine gastric mucosa, on a JEOL JSM35 (Japan) scanning electron microscope used in the secondary emission mode with an acceleration voltage of 25 kV. The images were captured digitally using ISCAN (ISS, Manchester, UK) hardware and software. Samples of porcine gastric tissue were inverted, mucosal side down, over a fine layer of cholestyramine particles to introduce the resin to the gastric mucosa. This was found to be adequate in providing a thin coating of resin on the mucosal surface, without clumping.

2.4. Data analysis

The tensile measurements between the test materials and the tissue were determined by the peak detachment force (mg) recorded when the disc became detached from the tissue. This detachment force was then calculated per mm^2 of tissue to take into account the surface area of the gastric mucosa available for mucoadhesion. The mean and standard error of the mean of twelve readings were then calculated per measurement.

As the data was normally distributed (determined using Minitab® for Windows Release 10.1 statistical package, Minitab), one-way analysis of variance (ANOVA) and two-sample *t*-Tests were carried out at a 95% confidence level to determine any statistical significant difference.

3. Results

The optimal values for the experimental parameters determined for both porcine and human mucosa were used in the subsequent experiments. These were defined as a contact time of 7 min, a separation rate of 3 mm/s and an applied force of 2.5 g for the porcine tissue and 3.0 g for the human tissue.

A typical scanning electron micrograph (SEM), taken of the cholestyramine in contact with porcine gastric mucosa, is given in Fig. 1. This shows the cholestyramine, magnified 480 times, embedded in the mucus layer of the porcine gastric mucosa. The particles were irregular in shape and representative of the particle size range.

From the particle size analysis carried out on samples from the three milled fractions, <40, 40–90, 90–125 μm, it was confirmed that 73.2% of the particles from the <40 μm fraction had a diameter of <40 μm, 81.8% of the particles in the 40–90 μm fraction had a diameter of between 40–90 μm, and finally 83.3% of the particles from the 90–125 μm fraction were found to have a diameter in the range 90–

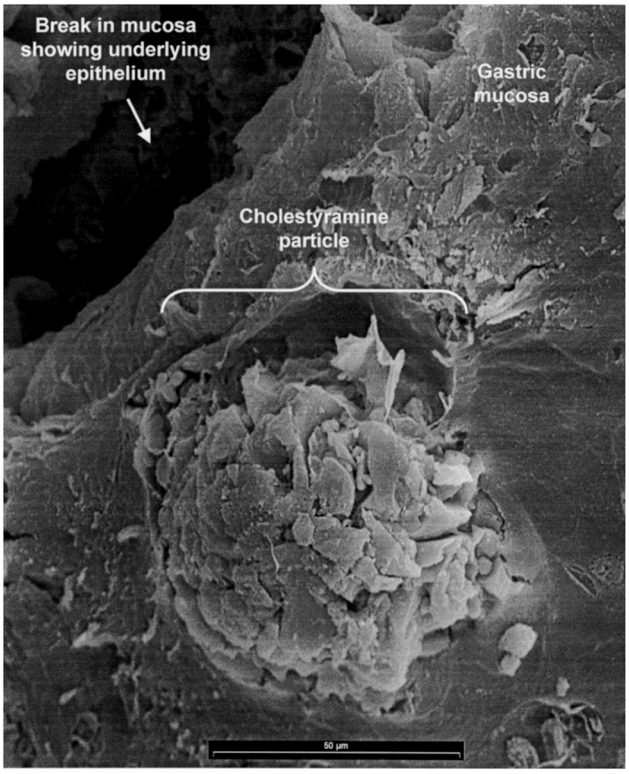

Fig. 1. SEM of cholestyramine embedded within the mucus layer covering porcine gastric mucosa.

125 μm. This was considered to be a suitable distribution for three discrete particle size fractions (Table 1).

As evident in Fig. 2, there was no significant difference between the three particle size ranges for mucoadhesion to either porcine or human gastric mucosa ($P = 0.673$ vs. 0.969 respectively). There was however a significant difference between the detachment forces recorded for porcine and human mucosa ($P < 0.5$).

The mean detachment forces required to pull two anionic exchange resins and three cationic exchange resins, all of similar particle size ranges, from both porcine and human gastric mucosa are given in Fig. 3. There was no significant difference in the detachment forces required to pull the anionic exchange resins from either porcine or human

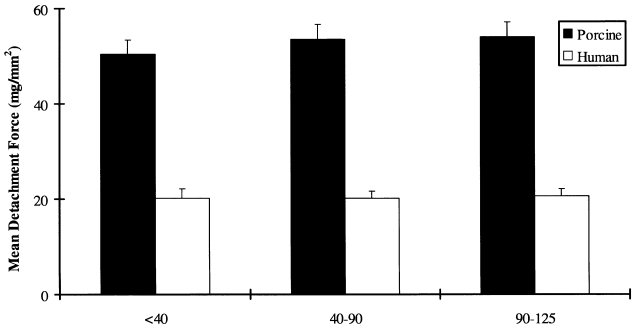

Fig. 2. Influence of resin particle size on mucoadhesion of cholestyramine ($n = 12$; mean ± SEM).

Table 1
Particle size analysis on three milled fractions of cholestyramine

Milled fraction with theoretical diameter (μm)	% of particles with actual diameter falling within milled fraction range
< 40	73.2
40–90	81.8
90–125	83.3

gastric mucosa (porcine, $P = 0.511$; human, $P = 0.307$); the mucoadhesion of CG-400 was similar to that of cholestyramine. There was also no significant difference within the cationic exchange resin group (porcine, $P = 0.469$; human, P-value 0.143). All three cationic exchange resins, IRP-69, CG-50 and IR-120, produced similar mucoadhesion forces. There was however a significant difference between the anionic and cationic exchange resins (porcine, $P = 0.0002$; human, $P = 0.0009$). The anionic exchange resins produced greater detachment forces. The mucoadhesion of cholestyramine to porcine mucosa was also significantly greater than to human gastric mucosa ($P = 0.03$).

Finally, the mucoadhesion of eight other test materials, in comparison to cholestyramine, is shown in Fig. 4a,b for porcine and human gastric tissue respectively. This shows a rank order of bioadhesion, with cholestyramine producing the second highest detachment forces, a detachment force of 54.03 mg/mm^2 from porcine mucosa and 30.45 mg/mm^2 from human mucosa. The known bioadhesives and gums, such as Carbopol and tragacanth, required high detachment forces to pull them from the mucosa, in the range of 30–60 mg/mm^2, whilst materials, such as dextran and polyethylene glycol, with detachment forces in the range of 17–22 mg/mm^2, showed no adhesive properties relative to the other test materials.

4. Discussion

Previous studies have shown that micronised ion exchange resins, in particular cholestyramine (Duolite® AP-143), administered as small volume suspensions, exhibit

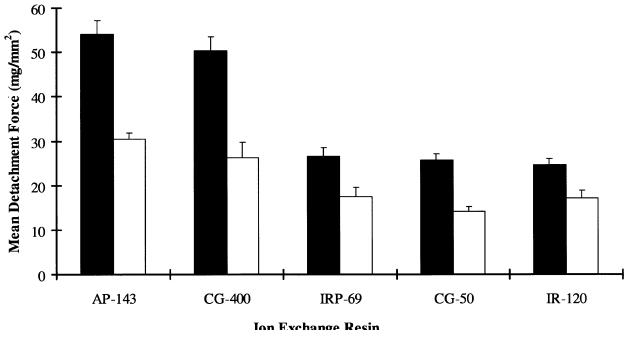

Fig. 3. Mucoadhesion of cholestyramine (AP-143) to gastric mucosa when compared to other ion exchange resins ($n = 12$; mean ± SEM: ■, porcine mucosa; □, human mucosa).

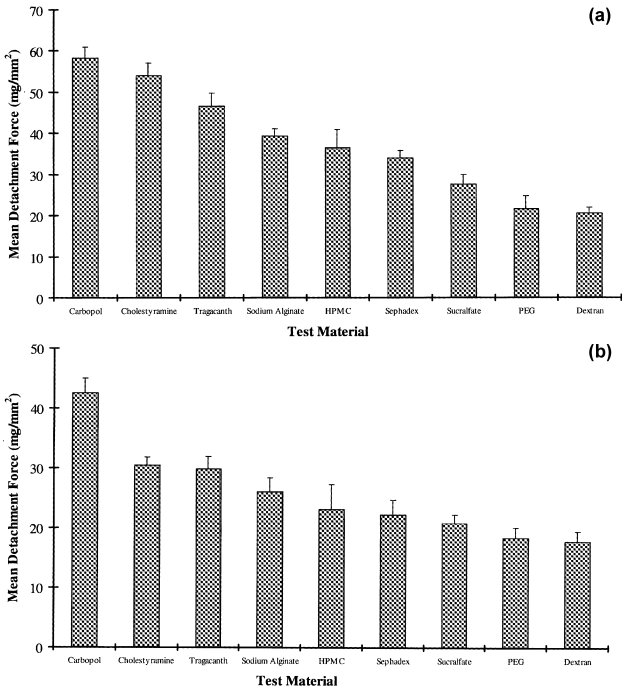

Fig. 4. Mucoadhesion of cholestyramine to (a) porcine gastric mucosa and (b) human gastric mucosa when compared to other test materials ($n = 12$; mean ± SEM).

extended gastric residence and have the ability to coat the gastric mucosa uniformly [1,2]. The mechanism for this was unclear although the suggestion that the resin was acting as a mucoadhesive was put forward. This study presented herein was designed to establish a system to investigate the potential mucoadhesion of cholestyramine and the factors affecting this using human gastric tissue and to compare this to animal tissue.

Tensile strength measurements from previous studies assessing the possible mucoadhesion of cholestyramine found that, although the system presented herein was able to perform reproducible peak detachment force measurements, these measurements were affected by instrumental parameters and the tissue surface area available for mucoadhesion [11]. As such, the optimal parameters were established in this present study prior to tensile testing and the measurements expressed in terms of the surface area of tissue available for mucoadhesion. The system used herein however could not reproduce conditions in the stomach, such as temperature, the presence of gastric juice or gastric pH, or take into account factors such as mucus turnover which is a prominent limiting factor of gastric bioadhesion in vivo. Some of these limitations may be overcome by immersing the system in media that may simulate gastric acidity and be temperature controlled, as used in other studies [7–9]. The perpendicular tensile stress exhibited here is also unlikely to occur in the stomach. Shear or peel forces, from the flow of gastric acid and contents or the contractile activity during phase III of the MMC, are more likely to be applicable in vivo. Despite its limitations, this system did however enable a comparison between test materials and particularly between established bioadhesives and potential bioadhesives.

To the authors' knowledge, there have been no investigations looking at bioadhesion to the gastric mucosa using excised human tissue. As previous in vivo studies assessing the gastric residence of cholestyramine were performed on healthy human volunteers, a model for mucoadhesion assessment to human gastric tissue was established. Preliminary studies looking at a direct comparison of porcine versus human gastric mucosa found that the forces of detachment of cholestyramine from porcine mucosa were significantly greater than from human mucosa ($P = 0.002$) [11]. Throughout these investigations, the detachment forces required with human gastric mucosa were lower, although not always significantly different from porcine mucosa. This could potentially be due to the differences in thickness of the mucus layer covering porcine and human mucosa. Although not measured, it was observed that the porcine mucosa was covered with a thicker layer of mucus than the human mucosa. This difference in mucoadhesion highlights a potential over-estimation of the degree of mucoadhesion when using animal tissue. A degree of variability in the detachment forces of cholestyramine to the gastric mucosa between studies under the same conditions was also observed. For example, the detachment force of cholestyramine from human mucosa in Fig. 2 was approximately 20 mg/mm^2, while under the same conditions in Figs. 3 and 4b, it was approximately 30 mg/mm^2. This could be due to the variability of the natural biological substrate. Unfortunately samples throughout the investigations could not be used from the same animal or patient. Tissue sections were limited and therefore so too were the number of samples obtained from these sections. Being a natural biological tissue, uniformity either in surface morphology, mucus covering or water content could not be guaranteed. Where possible, measurements within individual investigations were obtained from tissue excised from the same animal or patient to reduce variability.

It had been suggested that the extended gastric residence exhibited by cholestyramine was due to its small particle size, the particles becoming entrapped within the folds of the stomach [1]. Brown et al. however concluded that particle size per se was not responsible for gastric residence following their investigations with microparticles other than ion exchange resins [13]. As it has since been suggested that cholestyramine could extend gastric residence by mucoadhesion [2], it was thought that particle size could play a role in this potential mucoadhesion. Particle size could relate to the surface area available for mucoadhesion and this, along with mucus thickness, should be taken into account. Mikos et al. produced photomicrographs of particles with various diameters on mucus [18]. The smaller particles were embedded within the mucus layer, and would therefore have a greater surface area avail-

able to the mucus for mucoadhesion. The diameter of the larger particles exceeded the thickness of the mucus layer resulting in less surface area available and hence reduced mucoadhesion [18]. This present study concluded however that measured mucoadhesion is unaffected by particle size in the range between <40 μm and 125 μm. It is acknowledged that all the particle size fractions used were in the lower micrometer range and were less than the predicted mucus thickness; larger resin beads were not investigated. Had larger beads been studied, a reduction in mucoadhesion might have been observed. As evident in Fig. 1, the SEMs from this present study demonstrated that the cholestyramine particles were embedded well into the mucus layer and as such provided good mucoadhesion.

Anionic polymers have previously been shown to display better bioadhesive properties in vitro when compared to neutral or cationic polymers [14,15]. From the results presented here, the opposite appears true and indicates an alternative method of adhesion; the positively charged resins displayed greater bioadhesion than the negatively charged resins. The forces involved here in the mucoadhesion of the ion exchange resins are therefore more likely to be of an electrostatic nature; the force of attraction to the negatively charged mucus being due to the overall positive charge provided by the functional group of the resin. This was evident for both porcine and human gastric mucosa and gives an indication that the mechanism by which cholestyramine appears to be mucoadherent is related to surface charge. Thairs et al. however found no significant difference between the extended gastric residence of cholestyramine and the polymer-coated cholestyramine, designed to mask the surface charge, and concluded that surface charge was not a necessity and the extended residence was either solely a characteristic of the resin or was a function of the small particle size [2]. The results presented herein however would contradict this by showing that particle size does not have an effect on mucoadhesion in vitro but surface charge does. The similarities between the uncoated and coated resins in the Thairs data may have been due to incomplete masking of the surface charge on the resin. The assessment of surface charge on in vivo mucoadhesion of cholestyramine will be the focus of a further publication.

The tensile strength measurements of the detachment forces enabled a rank order of bioadhesion to both porcine and human gastric mucosa to be constructed. It should be highlighted however that this would be very dependent on the test conditions. The system was optimised for the investigation of cholestyramine but as previously mentioned each test substance may perform differently under varying conditions. The molecular weights of the materials, which were not recorded, could also affect the mucoadhesive performance [14] and should have been taken into account. Cholestyramine produced the second highest degree of mucoadhesion in comparison to eight other materials. This rank order was similar to those published by other groups [5,7,19] with Carbopol, sodium alginate, tragacanth and HPMC providing good mucoadhesion, and PEG (a neutral polymer) being less adhesive (Table 2). A large degree of mucoadhesion was expected from the compounds that formed gels on hydration such as Carbopol, tragacanth and sodium alginate. Sucralfate powder was chosen because of its apparent retentive properties when given to ulcer patients as a gel or a suspension [20]. The powder, however, did not form a gel on hydration and did not perform well, possibly as sucralfate has an affinity for ulcerative tissue rather than healthy gastric mucosa [21]. Sephadex, PEG and dextran, although not expected to perform well as bioadhesives, were chosen because of their similar particle size to that of the cholestyramine resin. Dextran and PEG required a lesser detachment force from the mucosa than the control disc. Again, this showed that particle size did not contribute to mucoadhesion. Two previous studies had shown that Amberlite® resins did not possess bioadhesive properties [7,8]. These studies however used the cationic

Table 2
Summary of the rank orders of bioadhesion produced by previous studies[a]

	Herein	Herein	Reference [19]	Reference [7]	Reference [5]
Model	Porcine gastric mucosa	Human gastric mucosa	Guinea-pig mucus	Rabbit mucosa	Guinea-pig mucus
Expression of results	Force (mg/mm^2)	Force (mg/mm^2)	Mean % force	Force (mg)	Mean % force
Rank Order	**Carbopol**	**Carbopol**	NaCMC	Polycarbophil	NaCMC
	Cholestyramine	**Cholestyramine**	**Tragacanth**	PHEMA	**Carbopol 934**
	Tragacanth	**Tragacanth**	**Sodium alginate**	Amberlite® 200 beads	**Tragacanth**
	Sodium alginate	**Sodium alginate**	Karaya gum	Gelatin	Gantrez
	HPMC	**HPMC**	Gelatin		**Sodium alginate**
	Sephadex	Sephadex	Pectin		Hypromellose
	Sucralfate	Sucralfate	PVP		Gelatin
	PEG	**PEG**	Acacia		Pectin
	Dextran	Dextran	**PEG 6000**		PVP
					Acacia
					PEG 6000

[a] Bold type represents crossover of materials between studies. HPMC, hydroxypropylmethyl cellulose; PEG, polyethylene glycol; NaCMC, sodium carboxymethyl cellulose; PVP, polyvinylpyrollidone; PHEMA, poly(hydroxyethyl methacrylate).

exchange resin, Amberlite® 200, which, being negatively charged, would also not have displayed good bioadhesion under the conditions in this system.

It can be concluded that in comparison to other known bioadhesives, cholestyramine exhibits good mucoadhesive behaviour to both porcine and human gastric mucosa under these specific in vitro conditions. It is postulated that the surface charge of the resin contributes to this behaviour but that resin particle size does not significantly affect this behaviour. In light of the findings presented herein, it could be postulated that the increased gastric residence of cholestyramine seen in previous in vivo studies could be due to the apparent mucoadherent behaviour of the resin.

Acknowledgements

The authors acknowledge Neena Washington for her initial input into the investigations and would like to thank Kate Bostock (Department of Surgery) for collection of the human gastric mucosa samples, Trevor Gray and the EM Unit (Department of Histopathology) for the SEMs of the resin and Clive Washington (Department of Pharmaceutical Sciences) for milling and particle sizing the resin fractions.

References

[1] S. Burton, N. Washington, R.J.C. Steele, R. Musson, L.C. Feely, Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa, J. Pharm. Pharmacol. 47 (1995) 901–906.

[2] S. Thairs, S. Ruck, S.J. Jackson, R.J.C. Steele, L.C. Feely, C. Washington, N. Washington, Effect of dose size, food and surface coating on the gastric residence and distribution of an ion exchange resin, Int. J. Pharm. 176 (1998) 47–53.

[3] S. Borodkin, Ion-exchange resin delivery systems, in: Polymers for Controlled Drug DeliveryCRC Press, Florida, 1951, pp. 215–230.

[4] W.J. Irwin, R. MacHale, P.J. Watts, Drug delivery by ion-exchange Part VII: Release of acidic drugs from anionic exchange resinate complexes, Drug Dev. Ind. Pharm. 16 (1990) 883–898.

[5] J.D. Smart, I.W. Kellaway, H.E.C. Worthington, An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery, J. Pharm. Pharmacol. 36 (1984) 295–299.

[6] S.A. Mortazavi, J.D. Smart, An investigation of some factors influencing the in vitro assessment of mucoadhesion, Int. J. Pharm. 116 (1995) 223–230.

[7] H. Park, J.R. Robinson, Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion, J. Control. Release 2 (1985) 47–57.

[8] H.S. Ch'ng, H. Park, K. Kelly, J.R. Robinson, Bioadhesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers, J. Pharm. Sci. 74 (1985) 399–405.

[9] J.D. Smart, An in-vitro assessment of some mucosa-adhesive dosage forms, Int. J. Pharm. 73 (1991) 69–74.

[10] M.J. Tobyn, J.R. Johnson, P.W. Dettmar, Factors affecting in vitro gastric mucoadhesion I. Test conditions and instrumental parameters, Eur. J. Pharm. Biopharm. 41 (1995) 235–241.

[11] S.J. Jackson, The use of ion exchange resins as potential bioadhesive drug delivery systems, PhD Thesis, University of Nottingham 1999.

[12] S. Leung, J. Robinson, Polymer structure features contributing to mucoadhesion II, J. Control. Release 12 (1990) 187–194.

[13] J. Brown, X. Ramtoola, I. Cumming, J. Butler, J.G. Devane, I.R. Wilding, What is the gastrointestinal transit of very small particles in humans? Proc. Int. Symp. Control. Rel. Bioact. Mater. 25 (1998) 126–127.

[14] S.A. Mortazavi, J.D. Smart, Factors influencing gel-strengthening at the mucoadhesive- mucus interface, J. Pharm. Pharmacol. 46 (1994) 86–90.

[15] K. Park, J.R. Robinson, Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion, Int. J. Pharm. 19 (1984) 107–127.

[16] H. BlancoFuente, B. VilaDorrio, S. Anguianoigea, F.J. OteroEspinar, J. BlancoMendez, Tanned leather – a good model for determining hydrogel bioadhesion, Int. J. Pharm. 138 (1996) 103–112.

[17] M.J. Tobyn, Factors affecting in vitro gastric mucoadhesion, PhD Thesis, University of Strathclyde 1994.

[18] A.G. Mikos, E. Mathiowitz, R. Langer, N.A. Peppas, Interaction of polymer microspheres with mucin gels as a means of characterising polymer retention on mucus, J. Colloid Interface Sci. 143 (1991) 366–373.

[19] J.D. Smart, I.W. Kellaway, In vitro techniques for measuring mucoadhesion, J. Pharm. Pharmacol 34 (1982) 70P.

[20] D. Vaira, C. Corbelli, G. Brunetti, M. Menegatti, M. Levorato, P. Mule, P. Colombo, M. Miglioli, L. Barbara, Gastric retention of sucralfate gel and suspension in upper gastrointestinal-diseases, Aliment. Pharmacol. Therap. 7 (1993) 531–535.

[21] T.E. Vasquez, H.T. Pretorius, G. Greenspan, Radiolabeled sucralfate – a review of clinical efficacy, Nucl. Med. Comm. 8 (1987) 327–334.