ELSEVIER

International Journal of Pharmaceutics 189 (1999) 81–89

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Comparative mucoretention of sucralfate suspensions in an everted rat esophagus model

D.J. Dobrozsi [a,*], R.L. Smith [b], A.A. Sakr [a]

[a] *College of Pharmacy, University of Cincinnati Medical Center, 3223 Eden Avenue, Cincinnati, OH 45267-0004, USA*
[b] *Bristol-Myers Squibb Pharmaceutical Research Institute, Exploratory Biopharmaceutics & Drug Delivery, New Brunswick, NJ, USA*

Received 6 May 1999; accepted 15 July 1999

Abstract

A simple, rapid, and reproducible in vitro model was established to quantify the relative esophageal mucoadhesive properties of viscous liquid formulations, and the model was applied to compare marketed sucralfate suspensions (Gastrogel, Antepsin, and Ulcogant) to better understand differences in clinical performance. Rat esophageal mucosal segments were everted onto a glass rod and briefly immersed into a liquid formulation containing ^{51}Cr microspheres. Indirect quantification of the retained formulation provided excellent recovery (98.7–101%) and reasonable precision (1.06–38.3% CV). Mucosal retention profiles of the formulations were determined by rinsing the coated tissue in relevant gastrointestinal fluids using the technique of reciprocating vertical immersion. Dispersions of the mucoadhesive hydrogel Carbopol 934P were employed to initially characterize the performance of the model with respect to composition of the rinse fluids, and type and amount of shear force during rinsing. Retention of Carbopol was sensitive to the mechanics of rinsing and to salivary salts but not mucin in the rinse medium. A sucralfate gel suspension (Gastrogel) showed much greater mucoadhesion and resistance to removal by saliva than two non-gel suspensions (Antepsin, Ulcogant). Results suggest that in situ gelation may be a contributing mechanism for strong esophageal retention. These in vitro results are in general agreement with published human esophageal retention data on similar sucralfate suspensions and lend credence to the everted rat esophagus as a qualitatively predictive in vitro model for development of esophageal mucoadhesive liquids.

Keywords: Carbomer; Esophagus; Mucoadhesion; Mucosal retention; Rat; Site-specific drug delivery; Sucralfate

1. Introduction

Site-specific drug delivery to the esophagus remains a relatively unexplored area of biopharmaceutics. Yet there are certain therapeutic areas,

* Corresponding author. Procter and Gamble, Health Care Research Center, 8700 Mason-Montgomery Rd., Mason, OH 45040-9462, USA. Tel.: +1-513-622-1211; fax: +1-513-622-2522.

E-mail address: dobrozsi.dj@pg.com (D.J. Dobrozsi)

0378-5173/99/$ - see front matter
PII: S0378-5173(99)00244-6

most notably the treatment of upper gastroesophageal disorders (e.g. gastroesophageal reflux, heartburn, dyspepsia, radiation-induced mucositis, and esophageal cancer), where prolonged drug retention within the esophageal region is often desired (Williams et al., 1987; Ito et al., 1990; Orlando, 1991; Taal et al., 1995). Furthermore, drug retention within the esophagus may expand the mucosal platform for gastric retentive systems for sustained delivery to the stomach and/or for extended systemic absorption in the GI tract. Lastly, pre-gastric drug absorption within the esophagus may provide a substantial contribution to the oral bioavailability of drugs that undergo extensive first pass metabolism.

The small epithelial surface area (estimated at 157 cm^2, from dimensions of Washington, 1991), rapid bolus transfer from the oropharynx to the stomach upon swallowing, and the need to maintain esophageal patency present barriers in the development of site-specific drug delivery systems in this region of the alimentary tract. In general, formulation approaches have focused on flowable systems, such as swallowable liquid and suspension dosage forms containing mucoadhesive polymers to impart retention on the esophageal mucosa. Because the conventional in vitro tensile test methods that have been used to study mucoadhesive polymers (as reviewed by Jimenez-Castellanos et al., 1993) are not especially useful for flowing liquids and suspensions, alternative models have been investigated. Iooss et al. (1995) have examined the retention and drug release in a continuous-flow column adhesion cell, and found the best retention for dispersions of polycarbophil, a mucoadhesive hydrogel. Ito et al. (1990) developed magnetic granules for delivery of anticancer agents to the esophagus which employed magnetism to target the granules during administration, and bioadhesive polymers to hold the granules there after removal of the magnet. This system employed an artificial esophagus model constructed from an agar tube, and the granules demonstrated some retention in vivo in rabbits (Nagano et al., 1997). Banning et al. (1998) examined esophageal mucosal adhesive properties of alginate dispersions using longitudinal sections of pig espohagus formed into an inclined trough. Some relationship was found between retention and specific carbohydrate content of the different alginates tested.

Whereas water-swellable polymers (both soluble and insoluble) have been the dominant focus of mucoadhesive drug delivery applications, the material most widely cited for its mucoadhesive properties to gastric mucosa is not a polymer at all, but a complex of aluminum hydroxide and sucrose octasulfate, i.e. sucralfate. Sucralfate is indicated for the treatment of gastric and duodenal ulcers (Ishimori, 1995), with a well-documented tenacious binding to normal and ulcerated mucosa in the stomach and small intestine, and with reported higher affinity at the ulcer sites (Morris, 1995). Unlike swellable polymeric mucoadhesives, such as polyacrylates, celluloses and poloxamers, the mechanism for the retention of sucralfate at mucosal surface is hypothesized to be due, in part, to its acid-induced chemical transformation from an insoluble powder to a swollen, adhesive 'paste' upon acidification in the stomach (Nagashima and Yoshida, 1979). The introduction of several swallowable suspension formulations of sucralfate and the reported binding to non-gastric mucosal surfaces suggest acidification may not be requisite for the mucoadhesive properties of sucralfate (Hardy et al., 1993; Vaira et al., 1993).

The objective of this work was to evaluate the relative in vitro esophageal retention of several marketed sucralfate suspensions with reported differences in gastric or esophageal retention, to better understand the formulation variables that may lead to substantive mucosal interactions. As part of this work, an everted rat esophagus model was established based on the model of Sakr et al. (1994). Important criteria in development of the model were that it permits testing of flowable systems with a wide range of viscosities, have high throughput, and be qualitatively predictive of human esophageal retention. The mucoadhesive polyacrylate hydrogel Carbopol 934P® was used in model development and as a comparator to sucralfate suspensions.

2. Materials and methods

2.1. Materials

Three different commercial sucralfate suspensions were obtained for testing from pharmacies in Europe: Antepsin (Wyeth, UK), Gastrogel (Bracco/Lisapharma, Italy), and Ulcogant (Merck, Germany). Each suspension contained 20% (w/v) sucralfate. Antepsin and Ulcogant contain in addition to sucralfate, glycerol, xanthan gum, flavor, sweetener, buffer, and preservatives in an aqueous suspension. Gastrogel is formulated as an aqueous suspension of sucralfate gel (Rossi et al., 1992), and excipients include sorbitol, sodium benzoate, sorbic acid, and flavor.

Carbopol 934P® was obtained from B.F. Goodrich Specialty Chemicals (Cleveland, OH, USA). ^{51}Cr-Labeled microspheres (NEN Life Science Products, Boston, MA, USA), had specific activity of 1.23 GBq/g, mean diameter of 11.2 μm, and were dispersed in an aqueous solution of 0.005% polysorbate 80 prior to use. Bovine submaxillary mucin type I and crude pig gastric mucin type II were obtained from Sigma (St. Louis, MO, USA). Stimulated human saliva was collected on ice from a single donor, frozen at −20°C until needed, and thawed at 4°C prior to use. The formula for simulated (artificial) saliva was adapted from Fusayama et al. (1963) and contained on a mg/ml basis: KCl 0.4; NaCl 0.4; Na2SO4 0.013; MgCl2 0.018; K2HPO4 4.2; KH2PO4 3.2, KOH 0.19. The simulated saliva also contained, when used, bovine submaxillary mucin at 3 or 4 mg/ml, and was prepared fresh and used the same day. The pH of simulated saliva at room temperature with and without mucin was 7.06 and 7.12, respectively. Simulated gastric fluid TS without pepsin (USP 23, 1995) was augmented with pig gastric mucin at 3 mg/ml, and had a measured pH of 1.17. All other chemicals and solvents were of reagent grade or purer.

2.2. Dispersion preparation and radiolabeling

The sucralfate suspensions were mixed well by shaking for 5 min prior to sampling. Carbopol was dispersed in water at 4% (w/w) by gentle overnight stirring, and centrifuged at approximately $2500 \times g$ for 10 min to remove entrained air. Carbopol or sucralfate dispersions were labeled with ^{51}Cr microspheres at approximately 28 kBq/g formulation by vigorous mixing and bath sonication. Homogeneity of the label in the formulations was determined by direct γ-scintillation of approximately 50 mg samples (coefficient of variation of $< 2.3\%$). Since the intent was to measure the formation of a coating layer of each formulation on the tissue, and then to follow loss of this layer, the ^{51}Cr microspheres were preferred over other radio-labeled markers tried in preliminary experiments ([^{3}H]mannitol and [^{14}C]polyethylene glycol 4000), because, as insoluble particles, erosion and desorption rather than diffusion into the rinse medium, will predominate in characterizing the loss due to rinsing. The microspheres were found to be uniformly dispersed within the Carbopol formulation by microscopy. Retention data from pilot experiments using these microspheres agreed with previous work in which chemical assay for aluminum by atomic absorption spectrophotometry was used as the marker of formulation retention for sucralfate (Fitzpatrick et al., 1995).

2.3. Esophageal binding and retention

To permit application of viscous liquids to a fresh, undisturbed esophageal mucosal layer, rat esophageal segments were everted and placed onto a glass rod according to a previous method used to study intestinal mucoadhesion of granules (Sakr et al., 1994). Male Sprague–Dawley rats (250–450 g, Charles River Laboratories, Portage, MI) were euthanized by CO2 inhalation, and the esophagus carefully dissected free. After quickly removing extraneous fat and connective tissue, it was either utilized immediately, or else placed in oxygenated, cold Krebs–Ringer bicarbonate buffer and used within 2 h. Each esophagus was dissected into 2-cm segments (total length was about 7–9 cm), everted onto a pair of forceps, and transferred to a 3-mm diameter glass rod which had a 4.5-mm ball tip to hold the tissue in place. The tissue was then placed into the rinse

medium at 37°C for an approximately 2-min equilibration period.

The tissues were then carefully immersed in the test formulations for 1 s to uniformly coat the mucosal surface. Pure glycerine was used as a Newtonian, viscous, non-adhesive control formulation. The weight of formulation initially coated on the tissue was determined, and the coated esophagus was then subject to rinsing in 12 ml of medium. For experiments with sucralfate suspensions, two different rinse conditions were used: simulated saliva with mucin as above, and also simulated gastric fluid. Gastric fluid was tested because in esophageal reflux disease gastric contents are refluxed back into the esophagus, thus playing a potentially significant role in the removal of any retained formulation.

Rinsing method, rinse velocity, and rinse medium composition were studied using the Carbopol dispersion as a model mucoadhesive hydrogel (Harris et al., 1990). The two rinse methods were reciprocating vertical immersion in a custom apparatus, or immersion and rotation using a type I/II USP dissolution tester. For vertical immersion, a rheostat attached to the apparatus permitted variation of the velocity by which the esophagus was immersed up and down in the rinse medium, and a range of 3.3–6.6 cm/s was used. These rates were chosen because, during a human swallow, the esophageal peristaltic contractile wave travels at a rate of from 2 to 6 cm/s (Washington, 1991). For immersion and rotation using the dissolution apparatus, a single speed of 135 rpm was tested. This speed was calculated to give a surface velocity of the spinning mucosa of 3.3 cm/s. The reciprocating vertical immersion method was used for testing of sucralfate suspensions, with a rate of 5.5 cm/s. The salient features of both rinsing apparatuses are illustrated in Fig. 1.

Four different rinse media were tested in experiments with Carbopol: water; human saliva, artificial saliva containing 4 mg/ml bovine submaxillary mucin; and an identical solution without mucin. The media were held at 37 ± 2°C and were sampled periodically throughout an experiment.

2.4. Radioassay and data analysis

^{51}Cr was determined by direct γ-scintillation using a Packard Minaxi Autogamma 5000 γ counter. After background correction, all count data were converted to equivalent mg of formulation using the assay data for the starting formulation. Total retained formulation was determined by summing the total radioactivity in all rinses and remaining on the tissue at the end of the experiment. Recovery was expressed as percent of retained formulation remaining on the tissue as calculated from the total mass determined from the radioactivity data, divided by the gravimetrically determined mass initially bound (prior to starting rinsing). Data were expressed either as percent remaining with the tissue of the total initial amount of formulation coated on to it, or as mass of formulation on the esophageal tissue.

3. Results and discussion

3.1. Ex vivo model development

Model development experiments were conducted using a 4% aqueous dispersion of the mucoadhesive hydrogel, Carobopol 934P.

3.1.1. Performance and recovery

Mass recovery for all tests of Carbopol averaged 98.7% (standard deviation, 5.01%), whereas recovery of glycerine was poorer and more variable (65%, standard deviation 31%). This was attributed to higher error in weighing the small amount of retained glycerine (7–12 mg) which coated the tissue initially, and to γ-scintillation uncertainty at very low radioactivity levels present in many of the samples for glycerine. Recovery for the sucralfate gel formulation Gastrogel averaged 101.5% (standard deviation, 1.8%). Precision of measurements was good at short times (high percentage retained on the tissue), but decreased as more of the formulation was rinsed off. After 3 min of rinsing, coefficient of variation for percent Carbopol formulation retained on the tissue was 1.06%, and after 95 min of rinsing 38.3% ($n = 6$).

3.1.2. Effect of mechanical rinse method

The vertical velocity of the tissues in the rinse medium was varied by a rheostat attached to the gear motor in the reciprocating vertical immersion (RVI) method. The effect of rinse method and velocity on the retention of 4% Carbopol rinsed in artificial saliva with mucin is shown in Fig. 2. Data for the viscous glycerine control are also shown.

Carbopol is more strongly retained to esophageal mucosa than glycerine, which is nearly completely rinsed from the tissue within 1 min. After 1 min of rinsing, 6% of the glycerine is retained, compared to 93.6% of the Carbopol formulation. There was no appreciable effect of rinse rate on the loss of Carbopol from the tissue when the reciprocating vertical immersion method was used. In contrast, rotation of the tissue immersed in rinse fluid using the dissolution apparatus resulted in much longer retention of formulation, even though the surface velocity of the tissue moving in the fluid was equivalent. By 95 min, 2.3% of the initial amount of Carbopol remained on the tissue rinsed by reciprocating immersion, whereas 47.9% remained on tissue rinsed by immersion and rotation. This suggests that the shear forces on the mucoadhesive layer are greater during reciprocating immersion than during rotation, which may be due to mechanical effects of the tissue repeatedly entering and leav-

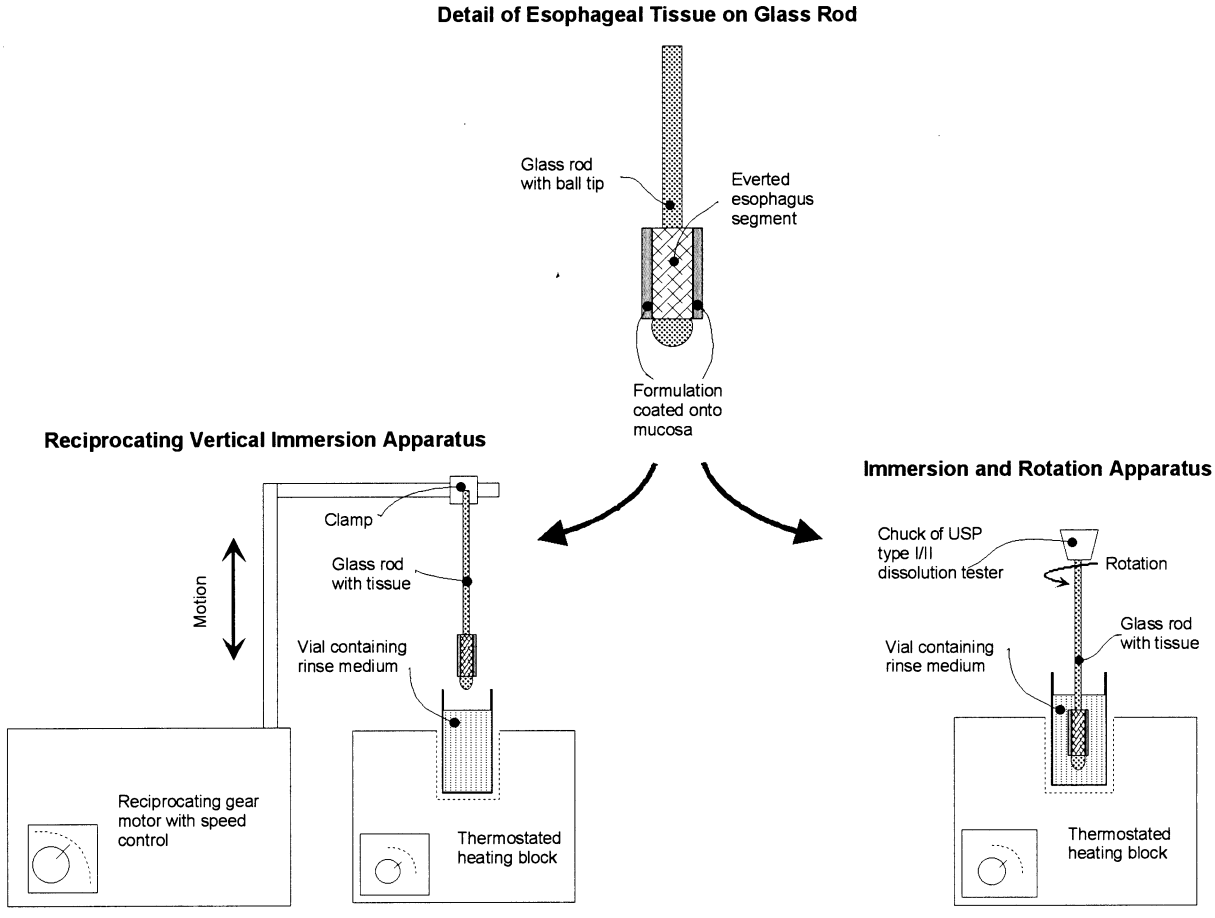

Fig. 1. Diagram of esophageal tissue everted onto the glass rod, and placement of this into the reciprocating vertical immersion (RVI) or immersion and rotation (IR) apparatus.

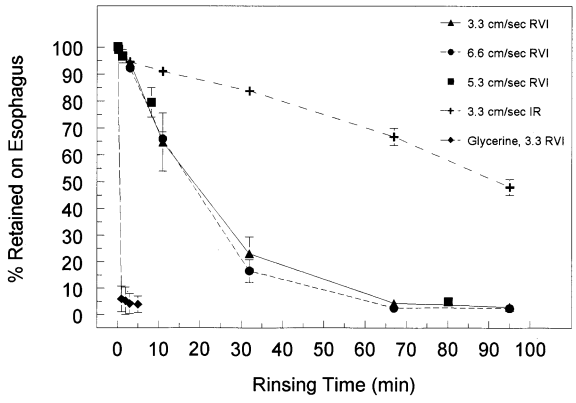

Fig. 2. Effect of rinse velocity and rinse apparatus on esophageal retention of Carbopol rinsed in artificial saliva with mucin. RVI, reciprocating vertical immersion method; IR, immersion and rotation using a dissolution apparatus. Velocity at the surface of the tissue during the test for each condition is given. Data are mean and standard deviation, $n = 4–6$.

ing the liquid surface. The RVI method appears more suited to those systems, which have reasonably strong mucosal retention (as is the case for sucralfate suspensions), whereas the immersion and rotational method may be more sensitive for evaluating liquid systems that have intrinsically low retention.

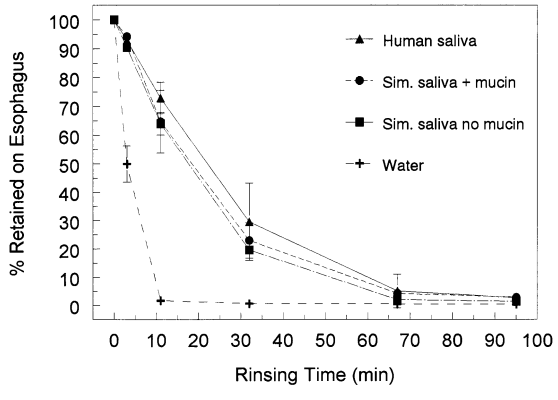

Fig. 3. Effect of rinse medium on esophageal retention of Carbopol rinsed at 3.3 cm/s by vertical immersion. Data are mean and standard deviation, $n = 4–6$.

3.1.3. Effect of rinse medium composition

The retention profile of a 4% Carbopol dispersion was similar when rinsing with human saliva, and the artificial saliva with and without mucin. Rinsing in water led to a more rapid loss of Carbopol from the tissue (Fig. 3). For example, after 11 min of rinsing, percent of initial retained was 72.9, 64.7, 64.0 and 1.8% for the human saliva, artificial saliva with mucin, artificial saliva without mucin, and water rinse media, respectively. Carbopol is a cross-linked polymer of acrylic acid, and aqueous Carbopol dispersions are known to undergo a large increase in viscosity upon neutralization with base. Since the Carbopol dispersions used in this study were not neutralized prior to treating the tissues (apparent pH of 3.5) and the salivas used as rinse media all have a pH close to 7 and significant buffer capacity, the in situ neutralization of the Carbopol upon tissue immersion is likely leading to an in situ gelation and, hence, longer retention. Water, with no buffer capacity, would not be able to gel with the Carbopol and therefore washes off more quickly. Carbopol is believed to be inherently mucin reactive, and rheological data on this interaction have been published (Tamburic and Craig, 1996). The mechanism of Carbopol adhesion to the mucosa reportedly involves a mucin–Carbopol chain inter-diffusion and binding (Leung and Robinson, 1992). However, in the work reported here mucin does not appear to be an important factor for in vitro retention of the formulation, as evidenced by the comparison of the artificial saliva data with and without mucin. A mechanism of gelation in situ may be a more important contributor.

3.2. Esophageal retention of sucralfate suspensions

Retention of the three sucralfate suspensions in response to rinsing with artificial saliva containing bovine submaxillary mucin are shown in Fig. 4. Gastrogel (106 mg $\pm$ S.D.) exhibited about twice the amount of initial coating on the tissue as Antepsin (51 mg $\pm$ S.D.) and 3.6 times as much as Ulcogant (29 mg $\pm$ S.D.). Upon subsequent rinsing, both Antepsin and Ulcogant were rapidly removed, whereas Gastrogel showed a prolonged

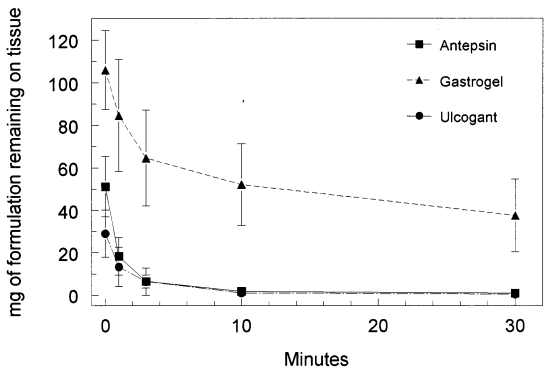

Fig. 4. Retention of three sucralfate suspensions rinsed by vertical immersion at 5.5 cm/s with artificial saliva containing 3 mg/ml salivary mucin. Data are mean and standard deviation, $n = 5$ or 6 per data point.

retention, with 35% of the initial amount bound to the esophagus after 30 min, compared to 1.7 and 1.1% for Antepsin and Ulcogant, respectively.

In contrast to the data with artificial saliva, the initial retention of the sucralfate suspensions on everted rat esophagus pre-treated with simulated gastric fluid (Fig. 5) showed comparable retention for Gastrogel (86 mg $\pm$ S.D.) and Antepsin (79 mg $\pm$ S.D.) and about 4-fold less for Ulcogant (19 mg $\pm$ S.D.). After 1 min rinsing with simulated gastric fluid, Gastrogel retention

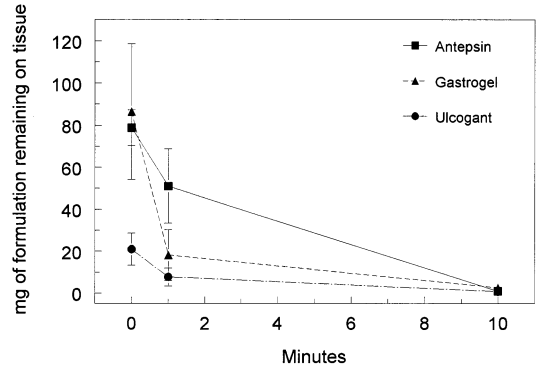

Fig. 5. Retention of three sucralfate suspensions rinsed by vertical immersion at 5.5 cm/s with simulated gastric fluid containing 3 mg/ml gastric mucin. Data are mean and standard deviation, $n = 4$ or 5 per data point.

was only 19% of the initial (18 mg $\pm$ S.D.), as compared to Antepsin (51 mg $\pm$ S.D., 64% of initial). Ulcogant was rapidly rinsed from the mucosa even at 1 min. After 10 min of rinsing with gastric fluid, only trace amounts remained on the tissue for any formulation.

Hardy et al. (1993) have shown, in a human scintigraphy study comparing the gastrointestinal transit of Ulcogant and Citogel (a sucralfate gel suspension), that the gel suspension had significantly greater esophageal retention (in seven of eight subjects, one for up to 60 min), whereas Ulcogant (which does not contain the gel form of sucralfate) was not retained in the esophagus at all. The difference in esophageal retention was significant. In the same study there was no significant difference between the formulations in terms of gastric retention. Goff et al. (1986) have reported significant esophageal retention of sucralfate obtained by pulverizing tablets and suspending in water only in subjects with esophageal ulceration, whereas subjects with normal esophageal mucosa showed no retention. Collectively, these clinical observations of various sucralfate suspensions are qualitatively consistent with the in vitro results obtained in the present study for the everted esophagus rinsed with saliva: sucralfate suspensions prepared with the gel form are more highly retained as compared to non-gel suspensions of sucralfate.

The suspension of sucralfate in gel form exhibits a strong rheological synergism with mucin as compared to suspensions of the non-gel form (Rossi et al., 1994; Dobrozsi et al., 1997). This suggests a possible mechanism for in situ gelation of the formulation on the tissue upon rinsing with mucin, which could explain the differences in the comparative retention observed in the present studies. An increase in viscosity induced by the rinsing agent (in this case, saliva) is similar to the Carbopol suspension which undergoes gelation via neutralization by buffer in the rinse medium. Rapid in situ gel formation induced by saliva components may provide a general mechanism around which to formulate esophageal retentive dosage forms.

4. Conclusion

The everted rat esophagus model permits a simple and rapid in vitro measurement of esophageal mucoretentive properties of viscous liquids. The method of reciprocating vertical immersion provides more vigorous shear force for removal of a formulation than immersion and rotation in a type I/II dissolution apparatus with rinse medium and rinsing method being important variables. Adjustments to the physiological rinse, such as pH or mucin type, may significantly influence the mucoretention, particularly for formulations that undergo pH- or mucin-dependent in situ gelation. This mechanism appears to play a substantive role in mucosal retention in vitro and may be important in vivo. Of the three sucralfate formulations evaluated, a suspension prepared from sucralfate in gel form was shown to have greater initial coating and retention on esophageal mucosa than suspensions not containing the gel form. These in vitro results are in agreement with published human esophageal retention data on similar sucralfate suspensions making this in vitro model qualitatively predictive for development of esophageal retentive liquid systems.

References

Banning, D., Craig, D.Q.M., Dettmar, P.W., Hampson, F.C., Onsøyen, E., 1998. An in vitro evaluation of the bioadhesive properties of sodium alginate solution on porcine esophagus. Annual Meeting Abstracts, American Association of Pharmaceutical Scientists. Pharm. Sci. Suppl. 1, S426.

Dobrozsi, D.J., Smith, R.L., Sakr, A.A., 1997. Effect of mucin type on sucralfate-mucin rheologic synergism in 3 suspensions. Pharm. Res. 14, S47.

Fitzpatrick, L.R., Best, K., Schussheim, M., O'Brien, L.M., Dobrozsi, D.J., 1995. A comparison of sucralfate and bismuth subsalicylate formulations in rabbit esophageal models. Gastroenterology 108, A94.

Fusayama, T., Katayori, S., Nomoto, S., 1963. Corrosion of gold and amalgam placed in contact with each other.' J. Dent. Res.42, 1183-1197.

Goff, J.S., Adcock, K.A., Schmelter, R., 1986. Detection of esophageal ulcerations with technetium-99m albumin sucralfate. J. Nucl. Med. 27, 1143–1146.

Hardy, J.G., Hooper, G., Ravelli, G., Steed, K.P., Wilding, I.R., 1993. A comparison of the gastric retention of a sucralfate gel and a sucralfate suspension. Eur. J. Pharm. Biopharm. 39, 70–74.

Harris, D., Fell, J.T., Taylor, D.C., Lynch, J., Sharma, H.L., 1990. GI transit of potential bioadhesive systems in the rat. J. Controlled Release 12, 55–65.

Iooss, P., Gouyetter, A., Le Ray, A.M., Patrice, T., Merle, C., 1995. Bioadhesive polymers as platforms for oral Barrett's oesophagus treatment, formulation and evaluation of various water-soluble bioadhesive polymers. Proc. 1st World Meeting APGI/APV, Budapest, pp. 829–830.

Ishimori, A., 1995. History of the development of Sucralfate. In: Hollander, D., Tytgat, G.N.J (Eds.), Sucralfate: From Basic Science to the Bedside. Plenum, New York, pp. 35–45.

Ito, R., Machida, Y., Sannan, T., Nagai, T., 1990. Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration. Int. J. Pharm. 61, 109–117.

Jimenez-Castellanos, M.R., Zia, H., Rhodes, C.T., 1993. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 19, 143–194.

Leung, S.S, Robinson, J.R., 1992. Polyanionic polymers in bio- and mucoadhesive drug delivery. In: Polyelectrolye Gels. American Chemical Society, Washington, DC, pp. 269–284.

Morris, G.P., 1995. Binding of sucralfate to the mucosal surface. In: Hollander, D., Tytgat, G.N.J (Eds.), Sucralfate: From Basic Science to the Bedside. Plenum, New York, pp. 71–82.

Nagano, H., Machida, Y., Iwata, M., Imada, T., Noguchi, Y., Matsumoto, A., Nagai, T., 1997. Preparation of magnetic granules containing bleomycin and its evaluation using model esophageal cancer. Int. J. Pharm 147, 119–125.

Nagashima, R., Yoshida, N., 1979. Sucralfate, a basic aluminum salt of sucrose octasulfate I: Behavior in gastroduodenal pH. Arzneim. Forsch. 29, 1668–1676.

Orlando, R.C., 1991. Sucralfate therapy and reflux esophagitis: an overview. Am. J. Med. 91 (Suppl. 2A), 123S–124.

US Pharmacopeia 23, 1995. US Pharmacopeial Convention, Rockville, MD, p. 2053.

Rossi, S., Bonferoni, M.C., Caramella, C., Colombo, P., Conte, U., 1992. Rheological study of sucralfate humid gel: a contribution to the comprehension of its stability properties. Eur. J. Pharm. Biopharm. 38, 78–81.

Rossi, S., Bonferoni, M.C., Caramella, C., Colombo, P., 1994. A rheometric method for assessing the sucralfate-mucin interaction. Eur. J. Pharm. Biopharm. 40, 179–182.

Sakr, A.A., Uraizee, S.A., Ritschel, W.A., 1994. An ex-vivo technique to evaluate the mucoadhesive strength of granules. Proc. Int. Symp. Control. Release Bioact. Mater. 21, 587–588.

Taal, B.G., Valdes Olmos, R.A., Boot, H., Hoefnagel, C.A., 1995. Assessment of sucralfate coating by sequential scintigraphic imaging in radiation-induced esophageal lesions. Gastrointest. Endosc. 41, 109–114.

Tamburic, S., Craig, D.Q.M., 1996. Thermogravimetric and thermorheological analysis of polymer/mucin mixtures. Pharm. Res. 9, S323.

Vaira, D., Corbelli, C., Brunetti, G., Menegatti, M., Levorato, M., Mulé, P., Colombo, P., Miglioli, M., Barbara, L, 1993. Gastric retention of sucralfate gel and suspension in upper gastrointestinal diseases. Aliment. Pharmacol. Ther. 7, 531–535.

Washington, N., 1991. Antacids and Anti-Reflux Agents. CRC Press, Boca Raton, FL, pp. 40–42.

Williams, R.M., Orlando, R.C., Bozymski, E.M., Readling, R.D., Castell, D.O., Roufail, W.M., Rick, G.G., Rubin, S.E., Sinar, D.R., 1987. Multicenter trial of sucralfate suspension for the treatment of reflux esophagitis. Am. J. Med. 83 (Suppl. 3B), 61–66.