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Research paper

Preparation and in vivo evaluation of mucoadhesive microparticles containing amoxycillin–resin complexes for drug delivery to the gastric mucosa

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Abstract

In this work, microparticles consisting of amoxycillin-loaded ion-exchange resin encapsulated in mucoadhesive polymers (polycarbophil and Carbopol 934) were prepared with the aim of increasing the efficacy of amoxycillin in the treatment of peptic ulcers by achieving targeted delivery to the gastric mucosa and prolonged drug release. An oil-in-oil solvent evaporation technique was conveniently modified in order to obtain polymer microparticles containing multiple amoxycillin–resin cores. Polycarbophil microparticles were spherical, Carbopol 934 microparticles irregular. In vitro release of amoxycillin was rapid with or without a polymer coating. Gastrointestinal transit in rats was investigated by fluorescence microscopy using particles loaded with fluorescein instead of amoxycillin: gastric residence time was longer, and the distribution of the particles on the mucosa apparently better, without any polymer coating.

Keywords: Polycarbophil; Carbopol 934; Mucoadhesive microparticle; Ion exchange resin; Gastrointestinal transit; *Helicobacter pylori*; Amoxycillin

1. Introduction

More than 50% of the pharmaceutical preparations on the market are for oral administration. The advantages of this route include the ease of administration, and avoidance of the pain and discomfort associated with injections. However, for drugs whose target is the stomach, such as antibiotics against *Helicobacter pylori* for local treatment of gastric ulcer, the development of oral drug delivery systems meets with physiological obstacles such as limited residence time and inefficient drug uptake by the gastric mucosa.

Helicobacter pylori is the main cause of both acute and chronic gastritis and peptic ulcer disease not associated with the use of non-steroidal anti-inflammatory drugs [1–3]. In vitro it is very sensitive to many antibiotics, especially the wide-spectrum aminopenicillin amoxycillin and certain macrolides such as clarithromycin. However, long-term monotherapy of gastric ulcer patients with amoxycillin is ineffective even at high daily doses, apparently due to limited contact time with the target site when administered in a conventional oral dosage form [4–7]. Local diffusion of the drug in the mucosa appears to be essential for achieving bactericidal levels in both healthy subjects [6] and patients: for example, Kimura et al. [8] achieved more complete eradication of *H. pylori* by applying a new method of topical therapy in which an amoxycillin solution was kept in contact with the stomach for 1 h. The development of oral amoxycillin dosage forms with prolonged gastric residence time is therefore an attractive goal.

Several strategies have been developed in order to prolong the gastric residence time of dosage forms and target the gastric mucosa, including the use of floating, swelling, expanding and bioadhesive forms [9–14]. For example, Burton et al. [13] found that in normal volunteers ion-exchange resins achieved excellent distribution in the gastric cavity and had a prolonged gastric residence time, 20–25% remaining for 5.5 h. More recent results by the same group indicate that the mechanism by which resin particles adhere to the mucosa is unlikely to be charge-based, since they persist in the stomach regardless of whether they bear a non-adhesive polymer coating and regardless of whether the stomach contains food [14]. Other authors have recently shown that ion-exchange resins

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also interact with other mucosal surfaces, such as the nasal mucosa [15].

The aim of the study described here was to improve the adhesion of ionic resins to the gastric mucosa by encapsulating them as microparticles in the mucoadhesive acrylic polymers polycarbophil and Carbopol 934. It was expected that improved adherence to the mucosa would both prolong gastric residence and result in more localized drug release. Efficient encapsulation procedures were developed, in vitro drug release from amoxycillin-loaded particles were characterized, and the gastric residence of fluorescein-loaded particles in rats was evaluated using fluorescence microscopy to monitor their gastrointestinal transit.

2. Materials and methods

The following chemicals were obtained from commercial sources and used as received: polycarbophil (Noveon AA1, B.F. Goodrich, Brecksville, OH, USA), Carbopol 934 (J. Escuder, Barcelona, Spain), amoxycillin trihydrate (Guinama, Valencia, Spain); anion-exchange resins in Cl^- form (Dowex 1-x4 and 1-x8, 200–400 mesh; Sigma, St. Louis, MO, USA), ethanol (Probus, Barcelona, Spain), liquid paraffin (intrinsic viscosity $>$ 110 mPa.s; Merck, Darmstadt, Germany); liquid paraffin (intrinsic viscosity 110–230 mPa.s; Analema, Vorquímica, Vigo, Spain), HPLC grade *n*-hexane (Romil, Cambridge, UK), stearyl alcohol (Pulcra, Barcelona, Spain), magnesium stearate (Claudio Barcia, Madrid, Spain), and sodium fluorescein (Sigma).

2.1. Purification of the ion-exchange resins

The resins were purified by rinsing about 10 g of wet resin successively with deionized water (3×50 ml), 95% ethanol (1×50 ml), 50% ethanol (1×50 ml) and deionized water (1×50 ml). Each rinsing stage lasted 1 h and was performed with magnetic stirring. The resins were then conditioned by cycling twice between the OH^- and Cl^- forms with 60 ml of 2 M NaOH and 60 ml of 2 M HCl, washing with deionized water after each treatment. Finally, the Cl^- form was isolated by vacuum filtration, washed thoroughly with deionized water, and dried to constant weight at 50°C in an electronic moisture balance (Shimadzu EB-280 MOC, Kyoto, Japan).

2.2. Loading of the resins

The purified resin particles (1 g dry weight) were suspended in an aqueous solution of amoxycillin containing a 25 equiv.% excess of drug with respect to the exchange capacity of the resins. After stirring at room temperature for 1 h the amoxycillin–resin complex formed was separated from the supernatant by vacuum filtration, washed with deionized water to remove unreacted drug, dried to constant weight and placed in a desiccator. Two batches of each amoxycillin–resin complex were prepared. For light microscopy, batches of Dowex 1-x4 loaded with methylene blue were prepared similarly.

The amoxycillin content of each complex was determined in duplicate by placing 50 mg of the dry complex into centrifugal basket stirrers with 400-mesh wire screens, which were introduced into 500 ml of acidic buffer (HCl/NaCl, pH 1.2, μ 0.1) and rotated at 1000 rev./min (IKA RW DZM, IKA Labortechnik, Staufen, Germany) at 37°C. The acidic medium was replaced every hour until the concentration of amoxycillin was negligible. The solutions from each sample were pooled and analyzed by ultraviolet spectrophotometry (229 nm) for amoxycillin content.

2.3. Preparation of polycarbophil microparticles

The amoxycillin-loaded resin particles (0.25 g) were suspended in a dispersion of the polymer (0.5 g) in ethanol (15 ml) and the suspension was emulsified in 100 ml of liquid paraffin (intrinsic viscosity $>$ 110 mPa.s) containing 0.8% w/v of magnesium stearate. The emulsion was then stirred at 1300 rev./min (IKA RW DZM, IKA Labortechnik, Staufen, Germany) until all ethanol had evaporated. The microparticles were isolated by vacuum filtration, washed with 200 ml of *n*-hexane, and air-dried for 24 h.

2.4. Preparation of Carbopol 934 microparticles

The polymer (0.3 g) and the amoxycillin–resin complex (0.15 g) were dispersed in ethanol (15 ml) and emulsified with liquid paraffin of intrinsic viscosity 110–230 mPa.s (100 ml) containing 1% w/v of magnesium stearate. After stirring at 500 rev./min until complete evaporation of the solvent, the microparticles were collected by vacuum filtration, washed with 200 ml of *n*-hexane, and air-dried for 24 h.

2.5. Morphology and size of microparticles

The surfaces and shapes of the microparticles were examined by scanning electron microscopy (Jeol JSM-6400, Tokyo, Japan). Samples were sputter-coated with gold for 165 s at 15 mA under argon (BAL-TEC SCD 004, Liechtenstein).

The size of the Carbopol microparticles was determined using a light microscope (Olympus BH 60, Tokyo, Japan) and an image analysis program (PC Image). That of the polycarbophil microparticles was determined by light microscopy (Olympus BH-2, Tokyo, Japan) by measuring 625 particles.

2.6. Drug release

In vitro release of amoxycillin from each formulation was determined at 37°C in a USP XXIII paddle apparatus operated at 50 rev./min. Coated or uncoated drug–resin complexes (150 mg) were stirred in dissolution medium consisting of 500 ml of acidic buffer (NaCl/HCl, pH 1.2, μ 0.1). At predetermined time intervals, 5-ml samples were

withdrawn, filtered and analyzed by ultraviolet spectrophotometry at 229 nm (Shimadzu UV-1603, Kyoto, Japan). Two replicates were performed for each batch of each formulation ($n = 4$).

2.7. Amoxycillin content of the microparticles

The total amoxycillin released from the microparticles by the end of the release assays (4 h) was taken as the drug content of the microparticles and expressed as a mass percentage with respect to the freshly coated drug–resin complex.

2.8. Gastrointestinal transit studies

The gastrointestinal transit of the coated and uncoated drug–resin complexes was evaluated in adult male Sprague–Dawley rats (200–300 g) using Dowex 1-x4 resin loaded with sodium fluorescein instead of amoxycillin. The fluorescein–resin complex was formed by suspending the purified resins in an aqueous solution of sodium fluorescein containing a 25 equiv.% excess of marker with respect to the ion-exchange capacity of the resin, and then stirring at room temperature for 24 h. The complex was isolated by vacuum filtration, washed with deionized water to remove unreacted fluorescein, and dried to constant weight. Two batches were prepared. Their fluorescein contents were calculated, following filtration, from the difference between the known content of the initial fluorescein solution and the final amount in the filtrate and the washings as determined by spectrofluorometry.

Microparticles were prepared by treating the fluorescein–resin complex as described above for the amoxycillin–resin complex.

Rats were fasted for 24 h before administration of the formulations, but were allowed free access to water. The fluorescein–resin complex (15 mg if uncoated, 45 mg if coated) was administered in 2 ml of water directly to the stomachs of conscious rats by means of a glass syringe fitted to a gastric cannula. After 1, 2 or 3 h, three rats were killed with ether, the stomach and small intestine of each were excised, and 3-cm segments of duodenum (initial part), jejunum (35 cm) and ileum (distal part above the caecum) were dissected free. The stomach and the intestine sections were opened lengthwise and observed under a fluorescence microscope.

3. Results

3.1. Formation of amoxycillin–resin complexes

Dowex 1-x4 and 1-x8 have, respectively, 4 and 8 % of divinylbenzene as cross-linker. Amoxycillin loading will have involved replacement of the OH^- group of the resin with the COO^- group of the amoxycillin. The less cross-linked resin, Dowex 1-x4, achieved the higher amoxycillin content (31.6%, as against 26.8% for Dowex 1-x8), and since drug release was rapid regardless of resin type, this was used in all subsequent work.

3.2. Encapsulation of amoxycillin-loaded resin in polycarbophil

To the best of our knowledge, there is only one report on the use of the oil-in-oil technique for the preparation of hydroxypropylcellulose–polycarbophil microspheres [16] We used a similar approach for the preparation of microspheres made of polycarbophil alone. We first optimized operating conditions in the absence of amoxycillin–resin particles. The conditions initially chosen (dispersion of 0.25 g of polycarbophil in 15 ml of ethanol and emulsification with 100 ml of liquid paraffin) led to the formation of aggregates rather than isolated particles, but addition of magnesium stearate to the paraffin allowed the formation of non-aggregated microspheres. Note that although ionic interaction between acrylic polymers and metal ions (Ca^{2+} or Zn^{2+}) has previously been reported [17,18], in our work the magnesium stearate appears to have a simple stabilizing role, since the salt will not have dissociated in liquid paraffin nor the polymer in ethanol. Therefore, the formation of such complexes was discarded.

Once the microencapsulation conditions were fixed, the drug–resin particles were incorporated into the inner phase of the emulsion in 2:1 coat-to-core mass ratio. Microscopical examination showed the formation of microparticles sized 94 ± 35 μm consisting of multiple drug–resin cores entrapped in a polymer matrix (Fig. 1a and Table 1).

Working under sink conditions, in vitro release of amoxycillin from the polycarbophil microparticles occurred very quickly, as in the case of the uncoated complex. Light micrographs of particles loaded with methylene blue (Fig. 2) show that the microparticles swelled considerably during

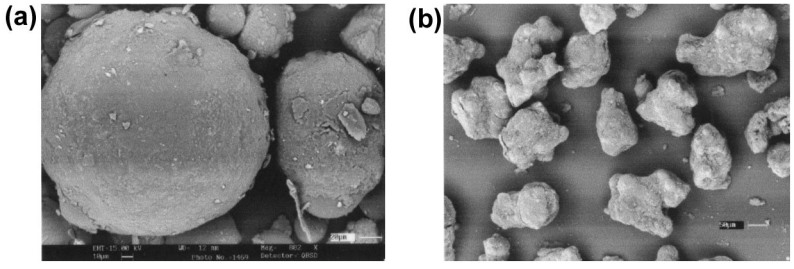

Fig. 1. Scanning electron micrographs of polycarbophil (a) and Carbopol (b) microparticles containing amoxycillin-loaded resin.

Table 1
Physical parameters of uncoated amoxycillin-loaded resin and acrylic microparticles

Formulation	Mean particle size (μm)	Amoxycillin content (%)
Amoxycillin–Dowex 1-x4 complex	–	31.56 ± 1.04
Polycarbophil microparticles	94 ± 35	8.50 ± 1.30
Carbopol 934 microparticles	133 ± 39	7.87 ± 0.35

incubation in the acidic release medium, but remained individualized. The swollen gel-like barrier around the drug–resin complexes did not limit diffusion and release of the amoxycillin.

3.3. Encapsulation of amoxycillin-loaded resin in Carbopol 934

Carbopol microparticles have previously been prepared by spray-drying [19], hot air suspension coating [20], spray-congealing [21] or solvent evaporation in a water-in-oil emulsion using high temperatures [22,23]. In this work we followed a similar approach except that, to avoid the need for high temperatures that might degrade amoxycillin, we formed an oil-in-oil emulsion, so that the evaporation of the solvent would be performed at room temperature. For adequate encapsulation of the drug–resin particles, it was necessary to use higher polymer and magnesium stearate concentrations and a more viscous liquid paraffin than for polycarbophil.

The resulting microparticles were very irregular in shape (Fig. 1b), and larger than with polycarbophil (mean particle size 133 ± 39 μm, see Table 1). As with polycarbophil, total amoxycillin release occurred within the first 15 min of the release assay.

3.4. Gastrointestinal transit of the formulations

Gastric residence was evaluated using fluorescein-labelled ion-exchange resin (fluorescein content 34.1 ± 1.3% w/w) and fluorescence microscopy to examine the distribution of the formulations in various sections of the gastrointestinal tract of rats 1, 2 and 3 h after administration. Figs. 3–5 show, for each time and tract region, selected micrographs obtained following administration of uncoated, polycarbophil-coated and Carbopol-coated resin particles, respectively. The gastric micrographs show parts of the glandular portion of the stomach because, although in the rodent stomach the glandular part is smaller than the non-glandular part (unlike the human stomach), this was the region in which most particles were found to accumulate.

After 1 h, the uncoated resin particles were located almost exclusively in the stomach, where they were distributed over the entire gastric surface (Fig. 3). After 3 h, some remained in the stomach but most had accumulated in the ileum.

Polycarbophil microparticles were also distributed throughout the gastric surface 1 h after administration, but as swollen aggregates rather than individual particles (Fig. 4); none had passed further down the gastrointestinal tract at this time. After 2 h, most had left the stomach and released their resin cores, which were found mainly bound to the jejunal mucosa; particles remaining in the stomach were found mainly in the glandular region. After 3 h, most resin particles were found in the ileum, although some still remained in the stomach.

Carbopol microparticles behaved similarly, except that a small number of resin particles were found in the duodenum and jejunum as early as 1 h after administration, and in two rats there were virtually no particles in the stomach after 3 h (Fig. 5).

4. Discussion

Experimental results on whether poly(acrylate) particles prolong the gastric residence of orally administered resins or protein beads have been mutually contradictory. Khosla and Davis [24] reported findings similar to ours: the co-administration of polycarbophil particles together with 500–1000 μm anionic resin particles to fasting humans did not prolong the gastric residence of the resin particles as determined by gamma scintigraphy. Likewise, Harris et al. [25,26] found that neither polycarbophil nor Carbopol particles had any

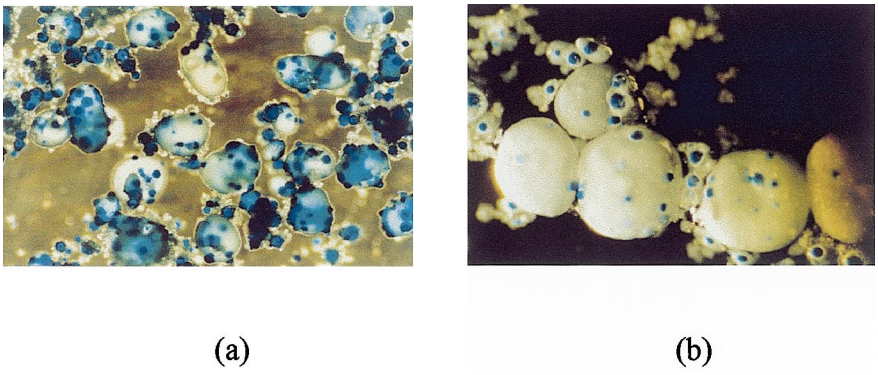

Fig. 2. Light micrographs of polycarbophil microparticles before (a) and after (b) a 4-h dissolution test.

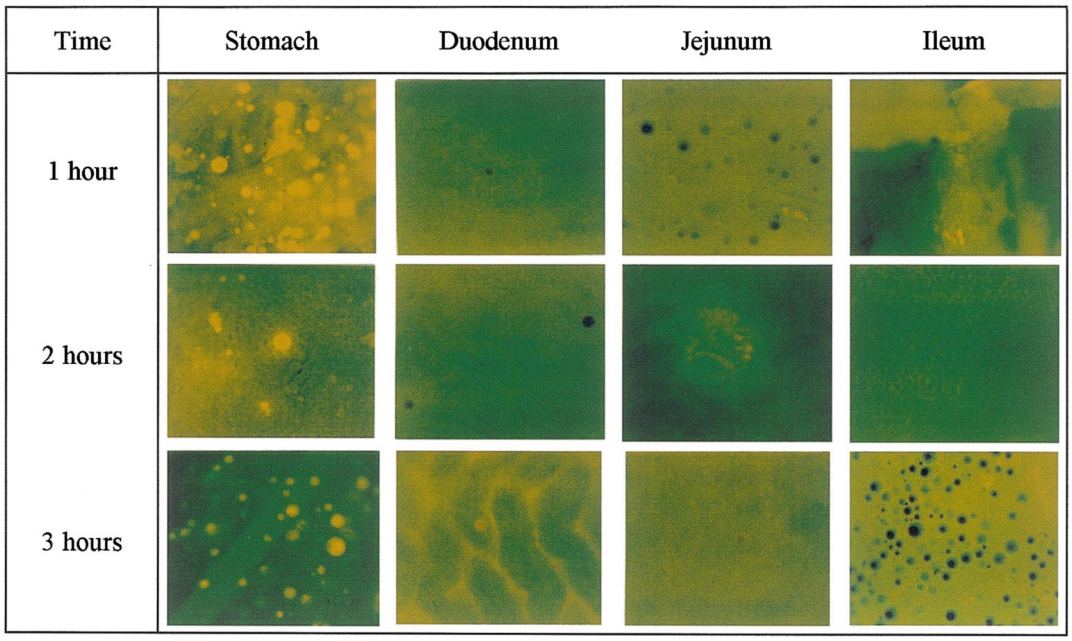

Fig. 3. Fluorescence micrographs of gastrointestinal segments at different times after oral administration of uncoated fluorescein-loaded resin.

effect on the gastric residence of radiolabelled resin beads. By contrast, Longer et al. [27] reported that the presence of polycarbophil increased the percentage of albumin beads retained for 6 h in the stomach of rats to nearly 90%; and although less prolongation of residence was obtained with dogs, this was attributed to the larger proportion of soluble mucins in the canine stomach [28]. Similarly, Ch'ng et al. [29] found that 9% of polycarbophil remained in the rat stomach for 24 h whereas emptying of 420–590 μm Amberlite 200 beads was complete after 6 h.

One likely cause of the discrepancies noted above is differences as regards the quantity of polymer administered: 70–150 mg (300–600 mg/kg) in the experiments of Longer et al. [27] and Ch'ng et al. [29] with rats, as against 100–250 mg (about 1.4–4 mg/kg) in those of Khosla and Davis [24] and Harris et al. [26] with human subjects. Since poly(acrylic acid) swells considerably at pH greater than its pK_a, the doses administered in the experiments with rats will probably have slowed gastrointestinal transit simply due to their bulk, rather than by improving adhesion to the gastric mucosa.

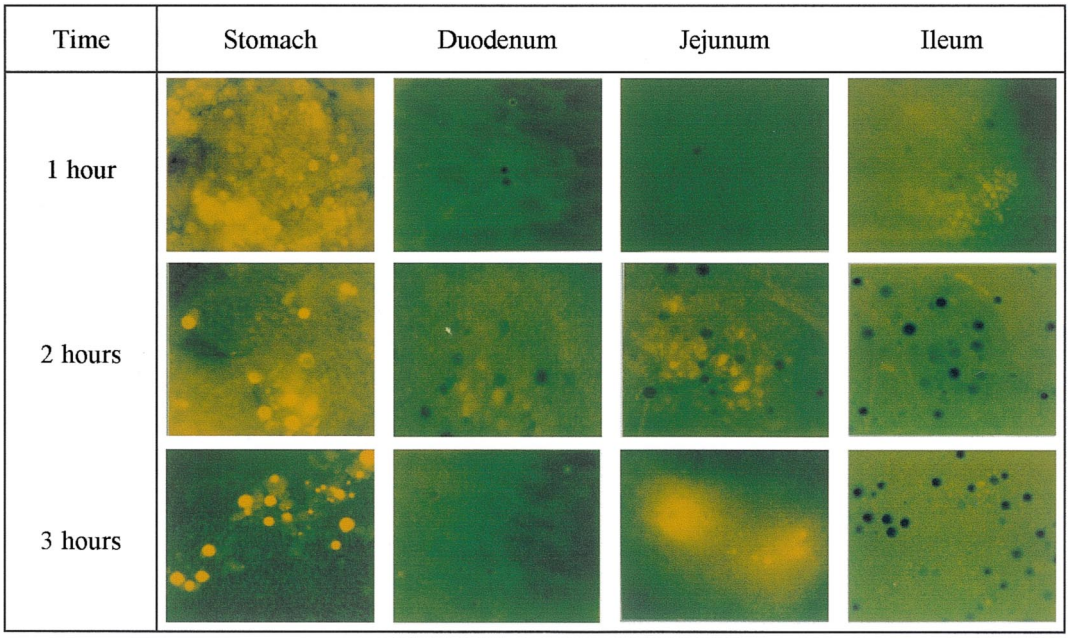

Fig. 4. Fluorescence micrographs of gastrointestinal segments at different times after oral administration of polycarbophil microparticles.

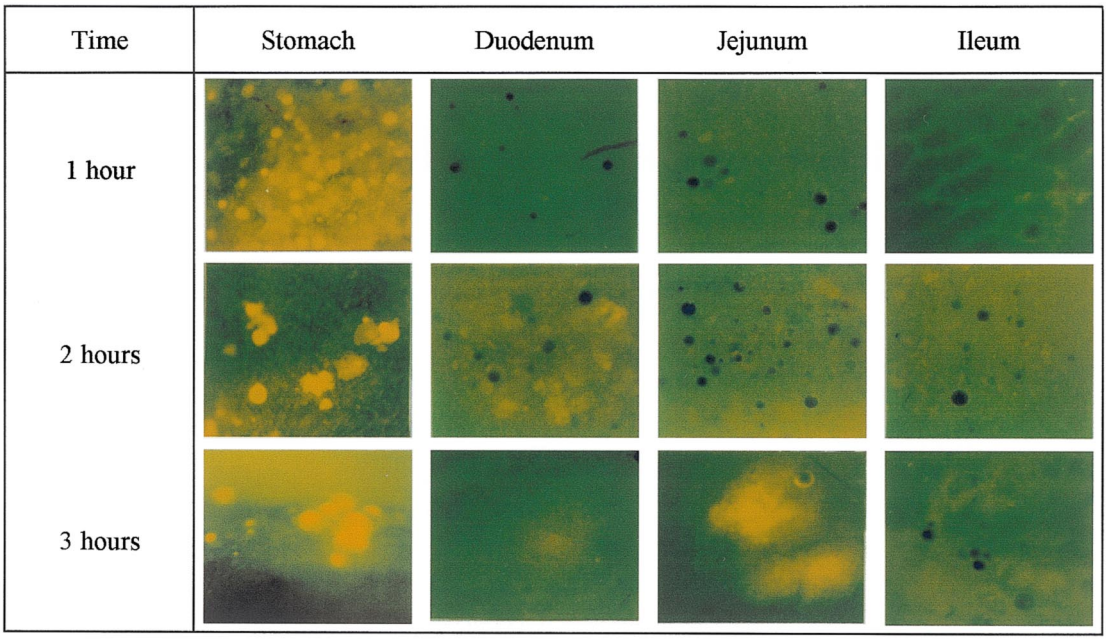

Fig. 5. Fluorescence micrographs of gastrointestinal segments at different times after oral administration of Carbopol microparticles.

Other experimental conditions that might affect gastric emptying include the volume of water used as vehicle in administering the formulation, and the use of anaesthesia. In our study, the polymer dose was 30 mg, i.e. 100–150 mg/kg, 2–6 times lower than in the experiments of Longer [27] and Ch'ng [29]; the formulations were administered in only 2 ml of water, a volume that is proportionally more similar to realistic administration volumes for humans than that used in Longer and Ch'ng's studies (4 ml; [27,29]); and there was no possibility of inhibition of gastrointestinal motility due to anaesthesia, which was not employed.

An important difference between the experiments mentioned above and ours is that whereas the former concerned physical mixtures of polymer and resin particles, we used resin cores entrapped in polymer microparticles, so that the adhesion of the resin to the mucosa was necessarily mediated by the polymer. Although Akiyama et al. [21,30] reported that Carbopol particles adhered to the stomach wall of rats for extended periods of time, the medium in which their particles were dispersed, a waxy base, may have prevented them from swelling as much as those used in our study. It seems likely that the swelling of the polymer in our experiments may have hindered anchorage of its chains in gastric mucus. This hypothesis agrees with the statement that although polymer chains need a certain degree of mobility in order to interpenetrate the mucus, the excessive mobility of the chains of greatly swollen polymers interferes with the entanglement process [31].

On the other hand, it has been claimed that mucoadhesive polymers associate more strongly with gastrointestinal mucus than do the mucin layers of the mucus with each other [32,33], and that it is therefore mucus turnover rather than mucin–polymer interaction that controls polymer transit through the gastrointestinal tract [34]. Since gastric motility and proteolytic activity make mucus turnover especially intense in the stomach [35], this may lead to gastric residence being short even for anionic polymers such as polycarbophil, which attach to mucus more strongly at the acidic pH values of the stomach than at neutral pH [29]. This could certainly be an explanation for our findings and also for those of a recent study in which polycarbophil particles were found to migrate through the gastrointestinal tract of rat at the same rate as non-adhesive Eudragit RL100 particles [36].

In conclusion, microencapsulation of ion-exchange resin particles in the mucoadhesive polymers polycarbophil and Carbopol 934 failed to prolong their residence in the stomach of rats to a significant extent. Like some previous findings [36], this suggests that non-specific mucoadhesive capacity may be irrelevant to the utility of a polymer as a component of a site-specific dosage form, at least when the target tissue is gastric mucosa. Furthermore, encapsulation in polycarbophil or Carbopol 934 appeared to favour the aggregation of the particles thereby making the distribution of particles in the stomach more difficult.

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References

[1] B.J. Marshall, J.A. Armstrong, D.B. McGechie, R.J. Clancy, Attempt to fulfil Koch's postulates for pyloric *Campylobacter*, Med. J. Aust. 142 (1985) 436–439.

[2] M.B. Fennerty, *Helicobacter pylori*, Arch. Intern. Med. 154 (1994) 721–727.
[3] J. Labenz, G. Boscg, Evidence for the essential role of *Helicobacter pylori* in gastric ulcer disease, Gut 35 (1994) 19–22.
[4] D.Y. Graham, G.M.A. Borsch, The who's and when's of therapy for *Helicobacter pylori*, Am. J. Gastroenterol. 85 (1990) 1552–1555.
[5] A. Ateshkadi, N.P. Lam, C.A. Johnson, *Helicobacter pylori* and peptic ulcer disease, Clin. Pharm. 12 (1993) 34–48.
[6] M.P. Cooreman, P. Krausgrill, K.J. Hengels, Local gastric and serum amoxycillin concentrations after different oral application forms, Antimicrob. Agents Chemother. 37 (1993) 1506–1509.
[7] J.C. Atherton, A. Cockayne, M. Balsitis, G.E. Kirk, C.J. Hawkey, R.C. Spiller, Detection of the intragastric sites at which *Helicobacter pylori* evades treatment with amoxycillin and cimetidine, Gut 36 (1995) 670–674.
[8] K. Kimura, K. Ido, K. Saifuku, Y. Taniguchi, K. Kihira, K. Satoh, T. Takimoto, Y. Yoshida, A 1-h topical therapy for the treatment of *Helicobacter pylori* infection, Am. J. Gastroenterol. 90 (1995) 60–63.
[9] N. Nagahara, Y. Akiyama, M. Nakao, M. Tada, M. Kitano, Y. Ogawa, Mucoadhesive microspheres containing amoxycillin for clearance of *Helicobacter pylori*, Antimicrob. Agents Chemother. 38 (1998) 2492–2494.
[10] A.K. Hilton, P.B. Deasy, In vitro and in vivo evaluation of an oral sustained-release floating dosage form of amoxycillin trihydrate, Int. J. Pharm. 86 (1992) 79–88.
[11] V.R. Patel, M.M. Amiji, Preparation and characterization of freeze-dried chitosan-poly(ethylene oxide) hydrogels for site-specific antibiotic delivery in the stomach, Pharm. Res. 13 (1996) 588–593.
[12] S. Shah, R. Qaqish, V. Patel, M. Amiji, Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for *Helicobacter pylori* infection, J. Pharm. Pharmacol. 51 (1999) 667–672.
[13] S. Burton, N. Washington, R.J.C. Steele, R. Musson, L. 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.
[14] S. Thairs, S. Ruck, S.J. Jackson, R.J.C. Steele, L.C. Freely, 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.
[15] M. Takenaga, Y. Serizawa, Y. Azechi, A. Ochiai, Y. Kosaka, R. Igarashi, Y. Mizushima, Microparticle resins as a potential nasal drug delivery system for insulin, J. Control. Release 52 (1998) 81–87.
[16] M. Bogataj, M. Burjak, A. Mrhar, Mucoadhesion of polycarbophil and chitosan microspheres on isolated guinea pig vesical and intestinal mucosa, J. Control. Release 48 (1997) 340–342.
[17] H.L. Lueßen, B.J. de Keeuw, D. Pérard, C.-M. Lehr, A.G. de Boer, J.C. Verhoef, H.E. Junginger, Mucoadhesive polymers in peroral peptide drug delivery. I. Influence of mucoadhesive excipients on the proteolytic activity of intestinal enzymes, Eur. J. Pharm. Sci. 4 (1996) 117–128.
[18] H.L. Lueßssen, J.C. Verhoef, J.G. Borchard, C.-M. Lehr, A.G. de Boer, H.E. Junginger, Mucoadhesive polymers in peroral peptide drug delivery. II. Carbomer and polycarbophil are potent inhibitors of the intestinal proteolytic enzyme trypsin, Pharm. Res. 9 (1995) 1293–1298.
[19] P. Vidgren, M. Vidgren, J. Arppe, T. Hakuli, E. Laine, P. Paronen, In vitro evaluation of spray-dried mucoadhesive microspheres for nasal administration, Drug Dev. Ind. Pharm. 18 (1992) 581–597.
[20] C.M. Lehr, J.A. Bowstra, J.J. Tukker, H.E. Junginger, Designing and testing of a bioadhesive drug delivery system for oral application, STP Pharma Sci. 5 (1989) 857–862.
[21] Y. Akiyama, N. Nagahara, Y. Kashikara, S. Hirai, H. Toguchi, In vitro and in vivo evaluation of mucoadhesive microspheres prepared for the gastrointestinal tract using polyglycerol esters of fatty acids and a poly(acrylic acid) derivative, Pharm. Res. 12 (1995) 397–405.
[22] M.D. Abd El-Hameed, I.W. Kellaway, Preparation and in vitro characterization of mucoadhesive polymeric microspheres as intra-nasal delivery systems, Eur. J. Pharm. Biopharm. 44 (1997) 53–60.
[23] A.M. Durrani, S.J. Farr, I.W. Kellaway, Precorneal clearance of mucoadhesive microspheres from the rabbit eye, J. Pharm. Pharmacol. 47 (1995) 581–584.
[24] R. Khosla, S.S. Davies, The effect of polycarbophil on the gastric emptying of pellets, J. Pharm. Pharmacol. 39 (1987) 47–49.
[25] D. Harris, J.T. Fell, H. Sharma, D.C. Taylor, Gastrointestinal transit of potential bioadhesive formulations in man: a scintigraphic study, J. Controlled Release 12 (1990) 45–53.
[26] D. Harris, J.T. Fell, D.C. Taylor, J. Lynch, H. Sharma, Gastrointestinal transit of potential bioadhesive systems in the rat, J. Control. Release 12 (1990) 55–65.
[27] M.A. Longer, H.S. Ch'ng, J.R. Robinson, Bioadhesive polymers as platforms for oral controlled delivery. III. Oral delivery of chlorothiazide using a bioadhesive polymer, J. Pharm. Sci. 74 (1985) 406–411.
[28] J.R. Robinson, M.A. Longer, M. Veillard, Bioadhesive polymers for controlled drug delivery, Ann. N. Y. Acad. Sci. 507 (1987) 307–314.
[29] H.S. Ch'ng, H. Park, P. 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.
[30] Y. Akiyama, N. Nagahara, E. Nara, M. Kitano, S. Iwasa, I. Yamamoto, J. Azuma, Y. Ogawa, Evaluation of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of furosemide and riboflavin, compounds with limited gastrointestinal absorption sites, J. Pharm. Pharmacol. 50 (1998) 159–166.
[31] R. Gurny, J.-M. Meyer, N.A. Peppas, Bioadhesive intraoral release systems: design, testing and analysis, Biomaterials 5 (1984) 336–340.
[32] J.R. Robinson, M.A. Longer, M. Veillard, Biological approaches to the controlled delivery of drugs, in: R.L. Juliano (Ed.), Annals of the New York Academy of Sciences, New York, 1987, pp. 307–314.
[33] S.A. Mortazavi, J.D. Smart, An investigation into the role of water movement and mucus gel dehydration in mucoadhesion, J. Controll. Release 25 (1993) 197–203.
[34] C.M. Lehr, J.A. Bouwstra, W. Kok, A.G. de Boer, J.J. Tukker, J.C. Verhoef, D.D. Breimer, H.E. Junginger, Effect of the mucoadhesive polymer polycarbophil on the intestinal absorption of a peptide drug in the rat, J. Pharm. Pharmacol. 44 (1992) 402–407.
[35] A. Allen, Structure and function of gastrointestinal mucus, in: L.R. Johnson (Ed.), Physiology of the Gastrointestinal Tract, Raven, New York, 1981, pp. 617–639.
[36] B. Tirosh, M. Baluom, T. Nassar, M. Friedman, A. Rubinstein, The effect of Eudragit RL-100 on the mechanical and mucoadhesion properties of polycarbophil dosage forms, J. Control. Release 45 (1997) 57–64.