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In vivo swelling kinetics of a series of hydrogel polymers in the cannulated gastrointestinal tract of the canine

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Abstract

Hydrogels for oral controlled drug delivery must swell as they move through the various regions of the gastrointestinal tract. Residence time in these different regions, coupled with available water and local environmental conditions, can potentially influence the rate and extent of swelling. The objective of this study is to regio-specifically study the in vivo swelling behavior of hydroxypropyl methyl cellulose, carboxylmethyl cellulose sodium salt, Carbopol 974P™, and Noveon AA1™ (polycarbophil) in the duodenal and ileal regions of the small intestine of cannulated canines in fasted and fed states. Atropine sulfate permitted the study of the influence of secretions on swelling. For each of the hydrogels studied, swelling was observed to be greater in the duodenum than the ileum with in vivo swelling not being strongly influenced by the fed condition or by the presence or absence of secretions. We propose that the fluid necessary for polymer swelling is primarily derived from the aqueous mucous gel coating the epithelial cells lining the small intestine. Differences in swelling rate and extent in ileal and duodenal regions may be due to differences in the amount and thickness of mucous in the two regions. © 1997 Elsevier Science B.V.

Keywords: Dog; Hydrogel; In vitro-in vivo correlation; Polymer swelling; Small intestine

1. Introduction

Hydrogels for oral controlled drug delivery must swell as they move through the various regions of the gastrointestinal tract in order to allow drug release. Residence time, coupled with available water and local environmental conditions in the different regions of the gastrointestinal tract, can potentially influence the rate and extent of this swelling. The inability to routinely develop good in vivo-in vitro correlations for oral controlled release products may, in part, be due to the absence of specific information on the availability of fluid in the different regions of the gastrointestinal tract.

The present research was undertaken to explore the in vivo swelling behavior of a series of hy-

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drogel polymers in the duodenal and ileal regions of the cannulated small intestine of the canine. This data is then compared to in vitro swelling behavior.

In the dry state, hydrogels are usually hard and glassy. Once swollen in water or body fluids they permit movement of drug out of the hydrogel network. The polymer is typically a cross-linked three dimensional network of chains. When immersed in a compatible fluid, the hydrogel expands by imbibing solvent. The cross-linking of the polymer chains prevents the gel from dissolving and the amount of swelling that occurs will depend upon the cross-link density of the polymer and its compatibility with the solvent (Siegel, 1990).

The ability of some hydrogels to absorb thousands of times their dry weight in water is due to the presence of hydrophilic groups such as -OH, -CONH, -$CONH_2$, -COOH and -SO_3H.(Peppas and Khare, 1993) The hydrogel character is determined by the hydrophilic monomers and density of the polymer network (Kudela, 1989).

Hydrogels can be neutral or ionic. The driving force for swelling in neutral hydrogels arises from the water-polymer thermodynamic mixing contribution to the overall free energy.(Peppas and Khare, 1993) The uncharged polymeric species swells due to functional groups that hydrate by forming hydrogen bonds with the imbibing water thus extending the polymer chains (Siegel, 1993). Water entry into the polymer network requires its expansion and consequently, an ordering of the polymer chains. Since the chains will be elongated into less entropically desirable configurations, they exert a resistive force. Swelling equilibrium occurs when the osmotic force driving water into the polymer is balanced by the resistive force exerted by the polymer chains.(Peppas and Khare, 1993; Ratner, 1981; Siegel, 1993) Since increasing cross-link density has the effect of increasing the resistive force to chain elongation, the more highly cross-linked a hydrogel polymer, the lower the degree of swelling observed (Ratner, 1981).

Studies were undertaken to examine swelling as a function of a number of dosing conditions. Thus, the value of ingested water, fed vs. the fasted state and the presence or absence of intestinal secrections were studied.

In choosing a model for our studies, an animal whose gastrointestinal system was similar to that of the human was needed. The animal choosen is the canine. In general, the gross anatomy and physiology of the gastrointestinal tract in humans and dogs are very similar. This is seen in the motility patterns, gastric pH, and the gastric emptying of liquids. A slightly higher intestinal pH in canines appears to be the main difference between the species in the fasted state. In addition, the canine is reported to have an overall shorter transit than the adult human and to have substantially more gastric mucus. However, various studies have shown that any concern about this difference may not be warranted (Dressman and Amidon, 1984; Ehrhardt et al., 1972; Lui et al., 1986).

2. Materials and methods

2.1. Materials

Noveon AA1™ (polycarbophil) and Carbopol 974P™ were a gift from B.F. Goodrich (Breckville, OH) and were used as received. Carboxymethyl cellulose sodium salt (NaCMC, Sigma, St. Louis, MO) and hydroxypropyl methyl cellulose (HPMC, Aldrich, Milwaukee, WI) were obtained commercially and used as received without further treatment. Pulmocare™, a high calorie, high fat, low carbohydrate liquid food was donated by the Ross Products Division of Abbott Laboratories (Columbus, OH). Atropine sulfate (0.4 mg/ml) was obtained from Eli Lilly (Indianapolis, IN). All other chemicals were either reagent or analytic grade and were used as received. Solution osmolarities were determined by a Wescor 5500 vapor pressure osmometer (Wescor, Logan, UT).

Three female mongrel hounds, with permanent intestinal cannulae, weighing between 17 and 27 kg, were used throughout the in vivo study. Lighting was maintained on a 12 h alternating cycle. The animals were fed a regular diet without any restrictions on the amount of water consumed.

2.2. Methods

2.2.1. Animal preparation

Modified Thomas type cannulae (Thomas, 1941) (The University of Wisconsin Physical Plant Machine Shop, Madison, WI) were constructed according to the modification of Rubinstein et al. (1988). Two cannulae were implanted into each canine. One was implanted in the duodenum approximately 20 cm distal to the pylorus and a second was implanted in the ileum approximately 20 cm proximal to the ileocecal junction. Prior to each study, the canines were fasted for at least 16 h overnight.

2.2.2. Sample preparation

Polymer swelling kinetics were studied using 18 mm flat diameter Spectra/Por 3 regenerated cellulose dialysis membrane with a molecular weight cut off (MWCO) of 3500 Dalton (Spectrum, Houston, TX). For each study, 155 mg of the desired polymer was inserted into a weighted (Eagle Claw split shot sinkers, Size #4, Taiwan) piece of dialysis tubing that was sealed at one end by 3-0 silk braided thread (Ethicon, Somerville, NJ). The second end of the tubing was then tied 4.0 cm from the first knot and trimmed to an overall length of 5.0 cm. This provided a constant surface area of 7.23 cm^2 and a constant internal volume of 4.15 cm^3 for all the samples used throughout this study.

A 30 cm piece of nylon line (Eagle Claw, monofilament fishing line, 20 lb. test, Brazil) was attached to one end of the dialysis bag permitting insertion, anchoring and recovery of the sample. The entire set up was weighed just prior to insertion of the polymer containing tubing into the medium of the study (in vivo or in vitro).

2.2.3. Statistical analysis

All results are expressed as the mean $\pm$ S.E. of the mean (SEM). Statistical analyses were performed using Statworks™ v. 1.2 (Cricket Software, Philadelphia, PA) and Statview™ v.1.0 (Brain Power, Calabasa, CA). Differences were considered significant when $p < 0.05$.

2.2.4. In vitro studies—Swelling as a function of surface area

The swelling nature of Noveon AA1 (polycarbophil) in water and isoosmotic phosphate and citrate buffers was studied in a series of dialysis membranes. The diameters of these membranes ranged from 11.5 to 28.6 mm corresponding to surface areas of 7.23 to 19.75 cm^2.

The tubing containing polymer was weighed just prior to being placed into 100 ml of a stirred solution of either water, simulated gastric fluid USP pH 1.2, isoosmotic citrate buffer pH 4.8, duodenal secretions pH 6.3 (collected from the fasted canines), isoosmotic phosphate buffer pH 7.2 or simulated intestinal fluid USP pH 7.5. The studies were conducted over a period of a minimum of 24 h. The amount of fluid sorbed by the polymer was measured by removing the tubing from the test solution, drying the excess external fluid by gently tapping onto a paper towel, and weighing. The above process was executed in less than 2 min to minimize evaporative loss. The grams of fluid sorbed i.e. the weight increase, divided by the weight of the dry polymer yielded a normalized extent of hydration.

2.2.5. In vivo swelling studies

In vivo swelling studies were executed in the dogs under both fasted and fed conditions. If the study was to be performed under fasted conditions, the dialysis tubing was inserted into the cannula of interest during phase I of the MMC without any further manipulations. However, if swelling was to be studied under fed conditions, 300 ml water or 8 oz (240 ml) Pulmocare™ (Ross Products Division of Abbott Laboratories, Columbus, OH) would then be administered directly into the stomach via a gavage tube immediately after insertion of the tube into the cannula. The liquid was injected at a rate so that all material was administered within 2 min. Total time from insertion of the dialysis tubing to completion of liquid administration was less than 5 min.

At an appropriate time, the cannula was opened and the dialysis tubing removed from the intestine. Excess intestinal material was gently wiped from the tubing with paper toweling and

the tubing weighed. Total time between removal to weighing was kept to under a minute to minimize any loss due to evaporation. Three to five repetitions of each experiment, i.e. each time point, were conducted for each canine. The results from the three dogs were pooled and the mean and S.E. calculated.

2.2.5.1. Oral ingestion of dialysis tubing. Two canines were placed in Pavlov-type slings, their duodenal cannulae opened and the effluent observed to establish true fasted conditions as verified by two phase III housekeeper waves of the MMC. The study was then performed using the dialysis tubing set up previously described using Noveon AA1™ (polycarbophil).

During phase I, i.e. 20 min after cessation of activity of the second phase III, the weighed tubing was swallowed naturally by the canine by being placed in the back of the throat and washed down with 50 ml of water equilibrated to room temperature. The volume of 50 ml was used because it is below the threshold of ≈ 150 ml where a fasted canine is converted to the fed state (Gupta, 1990).

The tubing was then allowed to freely pass from the stomach into the small intestine and was collected at the opened duodenal cannula. The time the dialysis tubing exited from the cannula was noted and the tubing weighed. The weight increase was normalized to the degree of hydration and plotted as a function of the time the tubing took to pass from the stomach to the duodenal cannula.

2.2.5.2. Loss on drying. An attempt to determine the relative amount of fluid in different intestinal regions led us to examine the loss-on-drying of material collected from the ileal and duodenal cannulae in both fasted i.e. no food, but free access to water and feed, i.e. free access to food and water, states.

The canines, fed or fasted, were placed in sling restraints and samples were collected from the intestine through the opened cannulae. Access to the contents of the intestinal lumen was accomplished through the use of a long handled spatula.

The material, on pre-weighed aluminum weighing pans, were placed in an oven at 100°C and heated until a constant weight was observed. The results were calculated as the percent of weight lost upon drying.

2.2.5.3. Swelling study in atropinized canines. Atropine sulfate (50 μg/kg) was administered to the fasted canine as an intravenous bolus 30 min prior to insertion of the dialysis tubing containing carboxymethyl cellulose, sodium salt. Subsequently, bolus booster injections of 30 μg/kg were given at intervals of 30 min for 2 h. The study was then continued without any additional atropine for a total of 6 h. The total atropine sulfate injected into each animal per study was 200 μg/kg. This dose is still higher than the literature value for the minimum required to shut down the secretory and motility patterns (AHFS Drug Information, 1991; Beglinger et al., 1981; Fox et al., 1983; Kayasseh et al., 1978; Konturek and Thor, 1986; Konturek et al., 1986; Lee et al., 1986; Pendleton et al., 1987) A wash out period of at least 72 h was permitted between studies.

The hydration curves generated in the atropinized animals were compared to curves generated in fasted, non-atropinized animals. Each time point was reproduced at least in triplicate for each canine, pooled and reported as the mean $\pm$ S.E.

Table 1
Comparison of in vitro rates of water sorption for Noveon AA1™ (polycarbophil) in a series of dialysis membranes of different diameters

Tubing diameter/mm	Water	Citrate buffer	Phosphate buffer
11.5	0.066	0.064	0.113
14.6	0.075	0.090	0.134
15.9	0.136	0.135	0.229
28.6	0.149	0.154	0.267

Rates are reported in g/h.

3. Results and discussion

3.1. In vitro swelling

As shown in Table 1, a direct relationship exists between the surface area of the tubing and the kinetics and extent of the amount of fluid sorbed by the polymer, polycarbophil. Predictably, the greater the surface area, the more fluid sorbed.

The results of the in vitro swelling studies for the different polymers in the various solutions are presented in Fig. 1A–D. Each point on the graphs represents the mean $\pm$ SEM of at least four individual experiments.

As can be seen in Fig. 1A, during the initial 8 h of hydration, the extent of swelling in water, ≈ 6.8 times dry polymer weight, was slightly more than in any of the other media, ≈ 5.3–6.0 times. In addition, water was the only medium whose swelling curve was seen to be statistically different. In examining the initial slope, i.e. for the first 6 h of the study, the rate of water uptake by HPMC was the same at the 99% significance level irrespective of the media studied. This showed, as would be expected for a neutral polymer, pH and ionic effects do not appear to affect the swelling behavior of the hydroxypropyl methyl cellulose.

It has often been observed that ionizable hydrogel polymers tend to swell more when they are ionized. This point is supported by examination of the extent and rate of swelling pictured in Fig. 1B in which the rate and extent of swelling for carboxymethyl cellulose differed are seen to be dependent upon the medium used.

In simulated gastric fluid, pH 1.2, the extent, ≈ 3.5 times dry polymer weight, and rate of swelling were significantly less than in any other medium. It appears that the acidic nature of the solution protonates the free carboxylate groups, which results in an overall minimizing of the repulsive force leading to reduced swelling or collapse of the polymer network. The hydration effect of the diffusing water molecules is lowered, resulting in reduced swelling.

When the diffusing medium was pure water, the extent, ≈ 25 times dry polymer weight, and rate of swelling were seen to be statistically more than in any other system studied. The remaining solutions were seen all grouped together, with similar swelling rates and extents, 10.9–13.3 times dry polymer weight. At 95% confidence, NaCMC swelled slightly better in the pH 7.2 phosphate buffer than in the other media, but still only about half of that seen in water alone. It appears that with a pK_a of approximately 4.0–4.7 a large portion of the carboxylic acid groups would be ionized in the media studied (pH range 4.8–7.5). The more ionized the polymer, the greater the effect of hydration, and the better the swelling.

The hydrogel polymers Carbopol and Noveon are very similar both chemically and structurally. Both polymers are large, with molecular weights $\approx 2 \times 10^6$ Da, lightly cross-linked with a high density of carboxylic acid groups. As with NaCMC, these polymers demonstrated the least swelling in acidic simulated gastric fluid (pH 1.2). As seen in Fig. 1C and D, the extent of swelling of Carbopol and Noveon, at 8 h, was seen to be 3.4 and 3.1 times the original dry polymer weight, respectively. In addition, each simulated gastric fluid curve was statistically different from that in any of the other media studied.

The only other statistically different curve was that generated in the pH 7.2 phosphate buffer swelling study. During the initial 8 h of the study in this buffer, Carbopol and Noveon sorbed enough fluid to result in weight increases of 6.6 and 7.8 times dry polymer weight, respectively. Since the pH 7.2 buffer is as much as 2.5 pH units above the pK_a of either polymer, it would be expected that the functional groups of the polyacid hydrogels would be more than 95% ionized.

The remaining studies resulted in weight increases of 4.5–5.5 and 3.5–5.1 times original dry polymer weight for Carbopol and Noveon, respectively.

3.2. In vivo swelling

There is a distinct difference in the degree of fluid uptake by the polymer in the duodenum versus uptake of fluid in the ileum. This is shown in Fig. 2A–D. Independent of whether the canine was fed or fasted, each polymer significantly sorbed more water in the duodenum than in the ileum. This is shown in Table 2 where the degree

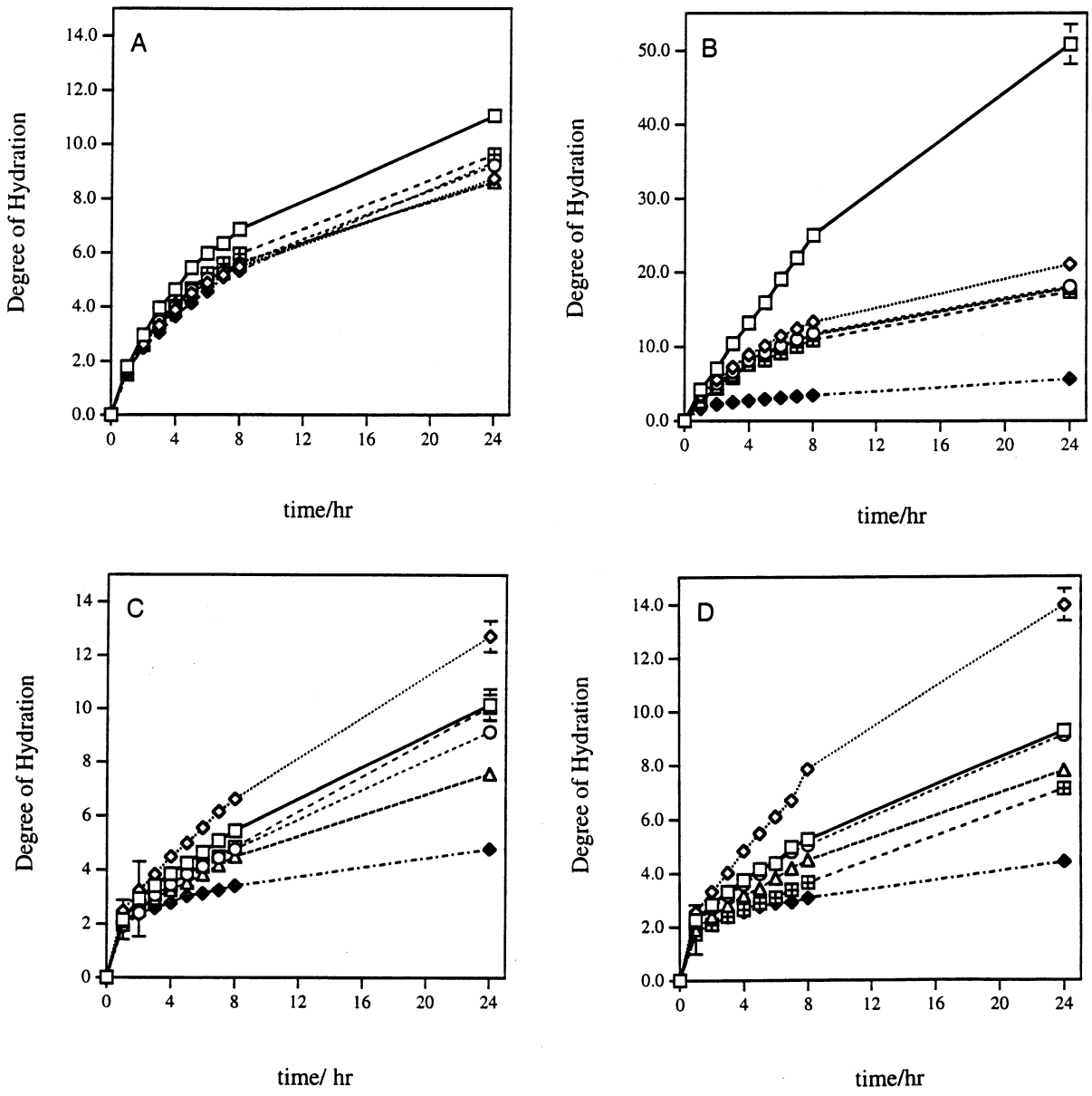

Fig. 1. In vitro swelling kinetics of hydroxypropyl methyl cellulose in a series of buffer media. Extent of hydration = (g of fluid sorbed)/(weight of dry polymer). Each point on the graph represents the mean ± SEM of at least four measurements. A: Hydroxypropyl methyl cellulose; B: Carboxymethyl cellulose sodium salt; C: Carbopol 974P™; and D: Noveon AA1™ (polycarbophil).

of hydration at 6 h is recorded for each polymer and each study condition.

It appears that the swelling of the polymer is governed much more by its regional position within the intestine than by the fluid it is exposed to. No differences were observed in swelling rate or extent for any of the polymers when the total amount of fluid as well as the three conditions of feeding (fasted, water, and Pulmocare™) was studied.

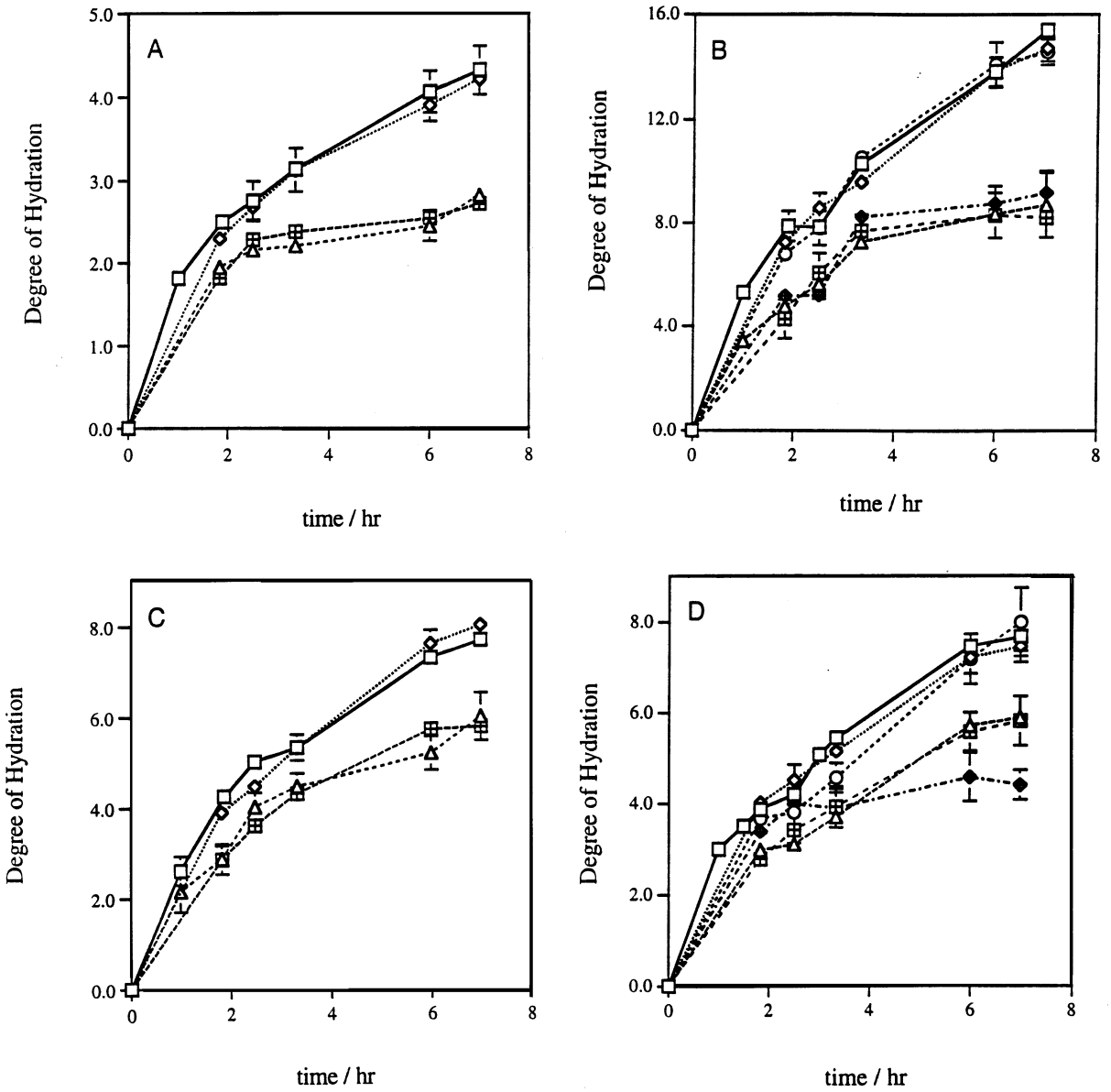

Fig. 2. In vivo swelling kinetics of polymer in the cannulated dog. Degree of hydration = (g of fluid sorbed)/(weight of dry polymer). Each point on the graph represents the mean ± SEM of at least six measurements. A: Hydroxypropyl methyl cellulose; B: Carboxymethyl cellulose sodium salt; C: Carbopol 974P™; and D: Noveon AA1™ (polycarbophil).

3.3. Oral ingestion of dialysis tubing

While an obvious linear relationship exists between weight increase and gastrointestinal residence time of the tubing, there are clear inter-animal differences, as shown in Fig. 3. The reason for these differences may be due to the age (2.5 versus 1 year), size (23 versus 17 kg) or differences in the time length of the phases of the MMC of each animal, especially phases I and II. (The total MMC cycle of each animal has been found to be essentially identical in each canine, ≈ 125 min).

Table 2
Comparison of the extent of swelling under fasted, fed and atropinized conditions after 6 h in the cannulated canine

Polymer	Duodenum				Ileum			
	Fasted	Water	Pulmocare	Atropine	Fasted	Water	Pulmocare	Atropine
HPMC	4.06	3.90	N.A.[a]	N.A.	2.45	2.54	N.A.	N.A.
CMC	13.82	13.83	14.09	13.55	8.34	8.30	8.76	10.50
Carbopol	7.27	7.58	N.A.	N.A.	5.17	5.70	N.A.	N.A.
Noveon	7.47	7.22	7.19	N.A.	5.73	5.58	4.58	N.A.

Degree of hydration = (weight of fluid sorbed)/(weight of dry polymer).
[a]N.A. = not available. Study not performed.

When the results of a swelling study for the orally ingested experiment were overlaid onto the results for polycarbophil directly inserted into a duodenal cannula, no significant difference was seen. It appears that polymer swelling is linearly dependent upon the gastrointestinal residence time and is less effected by local pH conditions.

3.4. Loss on drying

For the small sample studied the percent of water lost upon drying is shown in Table 3 to be significantly different for the regio-specific sampling for fasted, but not fed animals. It was also found that the percent lost upon drying was significantly different for the canines in the fasted as compared to fed state. Note that, in absolute terms, the differences in the values for the fasted ileum and the fed duodenum and ileum were essentially the same (89.6 versus 86.8%).

We conclude that while there may be a difference in fluid content in the material isolated from the lumen of the fasted canine, with more fluid found in the duodenum than the ileum, the difference does not seem to be very large. It is difficult to imagine that this is the primary source of the rate and extent of swelling differences described in earlier studies. The consistent differences seen in the regio-specific swelling (duodenum > ileum) are not fully explained by the very small differences in lumenal fluid content. These differences must be the result of a more defining property of the gastrointestinal tract.

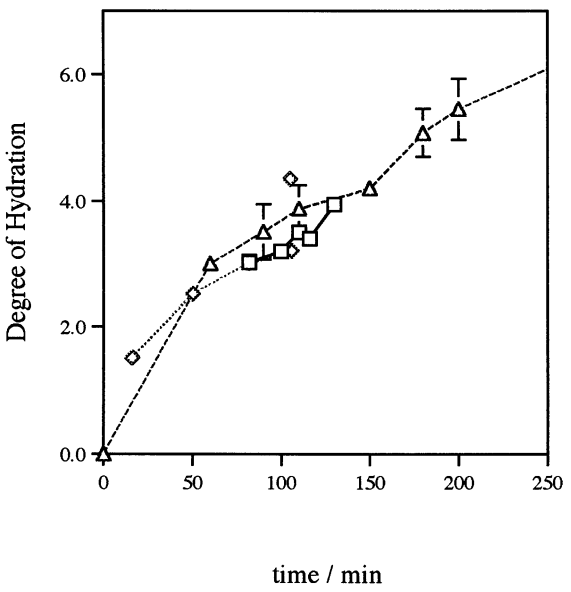

Fig. 3. In vivo swelling study in the canine. Oral ingestion of Noveon AA1™ (polycarbophil) filled dialysis tubing collected at duodenal cannula compared to similarly filled tubing inserted directly into duodenal cannula.

3.5. Swelling study with Atropine Sulfate

To study the effect of reduced fluid secretion on swelling, we chose the polymer that had previously shown the greatest sorption capacity under normal conditions, that is, carboxymethyl cellulose sodium salt. The hydration curves generated in the atropinized animals were compared to curves similarly generated in fasted, non-atropinized animals. The result of these studies is shown in Fig. 4 and Table 2. Each time point on the curves corresponds to the mean $\pm$ S.E. of a pool of at least three studies per canine, i.e. a minimum of nine data points.

Table 3
Loss on drying

	Region	*n*	Weight loss%	Standard deviation	Statistical significance
Fasted	Duodenum	8	96.8	1.17	Yes; $p<0.001$
	Ileum	7	89.6	1.34	
Fed	Duodenum	12	86.8	2.73	No
	Ileum	4	86.8	1.07	

The curves are essentially superimposable. Essentially no difference was seen in atropinized versus non-atropinized canines. The effect of gastric and duodenal secretions on the swelling of NaCMC appears to be minor. The only significant difference seen was for the ileum at $t=$ 6 h at which time, the swelling curve for the non-atropinized canines is seen to deviate from linearity as opposed to swelling curves for the atropinized animals that did not. This deviation was observed under both fed and fasted conditions.

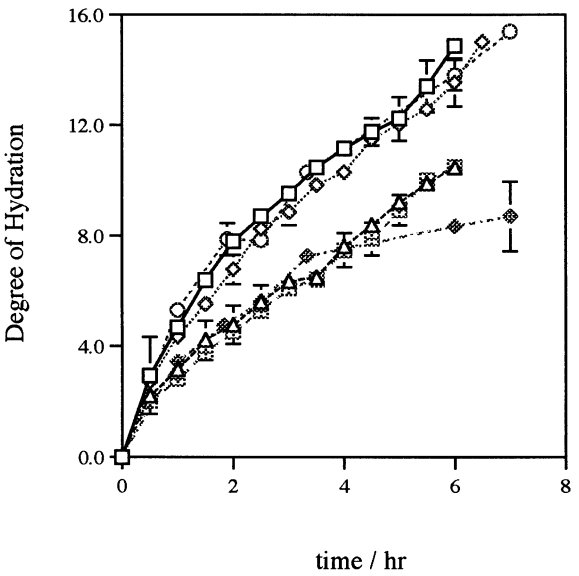

Fig. 4. In vitro swelling kinetics of carboxymethyl cellulose sodium salt in the atropine sulfate dosed canine. Degree of hydration = (g of fluid sorbed)/(weight of dry polymer).

4. Conclusions

The goal of this study was to add to the current understanding of the in vivo swelling behavior of hydrogel polymers. A fuller understanding of their often assumed unpredictable swelling nature in the gastrointestinal tract would assist in the design of more effective and efficient oral delivery systems.

The cannulated canine has been shown to be a good, albeit not perfect, model for human gastrointestinal studies. Fasted motility patterns and gastric emptying of liquids in canines are very similar to what has been measured in humans. Therefore, with the proper caveats, information acquired from canine studies can be applied to human subjects.

In vivo swelling studies have shown that, without exception, polymer swelling occurred to a greater extent in the duodenum as opposed to the ileum. In addition, swelling was found to be independent of whether the animal was fasted or fed water or Pulmocare™. This demonstrated that material emptied from the stomach is not a major source of fluid for swelling.

Studies performed, but not described here, showed that the extent of swelling of the polymer system placed directly into the intestine through the cannulae was seen to be independent of the timing of insertion relative to the migrating myoelectric complex (MMC). In addition, no difference was seen whether the polymer system was directly inserted into the duodenum or ingested orally and then allowed to pass through the pylorus into the duodenum naturally. The swelling kinetics was the same.

Swelling also does not appear to be affected by the presence or absence of gastrointestinal secretions. Through intravenous injections of atropine sulfate to shut down gastric and duodenal secretions, it is clear that hydrogel swelling was unaffected by secretions.

With these observations it appears that the source of fluid for polymer swelling is most likely the mucosal lining of the small intestine. A simple calculation was performed to try to approximate the amount of water that might be available in the mucous gel lining to a swelling polymer, at any particular moment. In order to make this estimate, we assumed a small intestinal surface area of 200 m^2, (Rao and Ritschel, 1995) a mucous layer composed of 95% water of uniform thickness at the upper limit of 500 μm (Allen et al., 1983), and a density of 1.0 g/cm. With these assumptions, we calculated that only 2.4 mg of water is available when a 4 cm long hydrogel delivery system is in intimate contact with the mucous layer and stationary within the small intestine. This is much lower than the values seen in our in vivo studies. Thus, a continuous supply of water to this mucus coat is needed.

Mucous is by nature 95% water and is kept fully hydrated through a dynamic equilibrium with water being supplied from the epithelial cells, the vascular bed and the lymphatic system (Allen, 1983; Creeth, 1982; Litt, 1984; Verdugo, 1984). It is not difficult to envision that an orally administered polymeric delivery system, residing within a collapsed intestine, would be in continuous, intimate contact with the mucous layer lining the epithelial cells. It would therefore be reasonable to assume that this intimate contact would result in the transfer of fluid required for polymer hydration. This assumption, that the mucous layer is the major source of swelling fluid, might also explain the difference in the rate and extent of swelling seen between the duodenal and ileal studies.

Studies on the intestinal tract of the rat (Altmann and LeBlond, 1970; Chu et al., 1995; Clarke, 1970; Rubinstein and Tirosh, 1994) have determined the thickness of the mucous gel layers in various regions of the intestinal tract. The mucous gel was found to be thickest in the duodenum decreasing gradually from the upper duodenum to the terminal ileum (Altmann and LeBlond, 1970; Clarke, 1970). In addition, it has been observed that the mucous secretion rate was significantly higher in the upper regions of the small intestine (Rubinstein and Tirosh, 1994).

Taken together, this evidence implies that a polymeric delivery system would be in contact with a greater amount of mucous in the duodenum than an identical delivery system situated in the ileum. More mucous implies more water available for hydration. Therefore, the result expected is exactly what has been observed. The rate and extent of swelling of identical polymers would be greater in the duodenal region of the small intestine than in the ileum.

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References

AHFS Drug Information, 1991. G.K. McEvoy, (Ed.), Bethesda, MD. American Society Hospital Pharmacists, pp. 653–656 and 1664–1665.

Allen, A., 1983. Mucus-a protective secretion of complexity. Trends Biochem. Sci. 8, 169–173.

Allen, A., Hutton, D., McQueen, S., Garner, A., 1983. Dimensions of gastroduodenal surface pH gradient exceed those of adherent mucus gel layers. Gastroenterology 85, 463–476.

Altmann, C.G., LeBlond, C.P., 1970. Factors influencing villus size in the small intestine of adult rats as revealed by transposition of intestinal segments. Am. J. Anat. 127, 15–36.

Beglinger, C., Haecki, W., Gyr, K., Stalder, G.A., 1981. The release of pancreatic polypeptide by intraduodenal l-phenylalanine in the dog. Hepato-Gastroenterolgy 28, 116–117.

Chu, K.U., Tsuchiya, T., Ishizuka, J., Uchida, T., Townsend, C.M. Jr., Thompson, J.C., 1995. Tropic response of gut and pancreas after ileojejunal transposition. Ann. Surg. 221, 249–256.

Clarke, R.M., 1970. Mucosal architecture and epithelial cell production rate in the small intestine of the albino rat. J. Anat. 107, 519–529.

Creeth, J.M., 1982. Constituents of mucus and their separation. Br. Med. Bull. 34, 17–24.

Dressman, J.B., Amidon, G.L., 1984. Radiotelemetric method for evaluating enteric coatings. J. Pharm. Sci. 73, 935–938.

Ehrhardt, L., Hartmann, V., Patt, L., 1972. Deutsche Apotheker-Zeitung 112, 2005.

Fox, J.E.T., Daniel, E.E., Jury, J., Track, N.S., Chiu, S., 1983. Cholinergic control mechanisms for immunoreactive motilin release and motility in the canine duodenum. Can. J. Physiol. Pharmacol. 61, 1042–1049.

Gupta, P.K., 1990. Processing of Liquids and Solids by the Fasted Canine Stomach. Doctor of Philosophy thesis, University of Wisconsin–Madison.

Kayasseh, L., Haecki, W.H., Gyr, K., Stalder, G.A., Rittmann, W.W., Halter, F., Girard, J., 1978. The endogenous release of pancreatic polypeptide by acid and meal in dogs. Effect of somatostatin. Scand. J. Gastroenterol. 13, 385–391.

Konturek, S.J., Thor, P., 1986. Relation between duodenal alkaline secretion and motility in fasted and sham fed dogs. Am. J. Physiol. 251, G591–G506.

Konturek, S.J., Thor, P., Bilski, J., Tasler, J., Cieszkowski, M., 1986. Cephalic phase of gastroduodenal alkaline secretion. Scand. J. Gastroenterol. 21 (125), 100–105.

Kudela, V., 1989. Hydrogels. In: Kroschwitz, J.I. (Ed.), Polymers: Biomaterials and Medical Applications. Wiley, New York, pp. 228–252.

Lee, K.Y., Shiratori, K., Chen, Y.F., Ta-Min, C., Chey, W.Y., 1986. A hormonal mechanism for the interdigestive pancreatic secretion in dogs. Am. J. Physiol. 14, G759–G764.

Litt, M., 1984. Comparative studies of mucus and mucin physicochemisty. In: Jonathan, N., O'Connor M. (Eds.), Mucus and mucosa. Ciba Foundation symposium 109, London, Pittman, pp. 196–211.

Lui, C.Y, Amidon, G.L., Berardi, R.R., Fleisher, D., Youngberg, C., Dressman, J.B., 1986. Comparison of gastrointestinal pH in dogs and humans: implications on the use of the beagle dog as a model for oral absorption in humans. J. Pharm. Sci. 75, 271–274.

Pendleton, R.G., Bendesky, R.J., Cook, P.G., 1987. Effects of Atropine upon various components mediating postprandial gastric acid secretions in dogs. J. Pharmacol. Exp. Met. 240, 396–399.

Peppas, N.A., Khare, A.R., 1993. Preparation, structure and diffusional behavior of hydrogel in controlled release. Adv. Drug Delivery Rev. 11, 1–35.

Rao, S., Ritschel, W.A., 1995. Colonic drug delivery of small peptides. S.T.P. Pharma Sciences 5, 19–29.

Ratner, B.D., 1981. Biomedical applications of hydrogels; Review and critical appraisal. In: Williams, D.F. (Eds.), Biocompatibility of Clinical Implant Materials: CRC Series in Biocompatibility, Boca Raton, FL, CRC Press, pp. 145–175.

Rubinstein, A., Li, V.H.K., Gruber, P., Bass, P., Robinson, J.R., 1988. Improved intestinal cannula for drug delivery studies in the dog. J. Pharmacol. Met. 19, 213–217.

Rubinstein, A., Tirosh, B., 1994. Mucus gel thickness and turnover in the gastrointestinal tract of the rat: Response to cholinergic stimulus and implication for mucoadhesion. Pharm. Res. 11, 794–799.

Siegel, R.A., 1990. pH-Sensitive gels: Swelling equilibria, kinetics, and applications for drug delivery. In: Kost, J. (Ed.), Pulsed and Self-Regulated Drug Delivery. Boca Raton, FL, CRC Press, pp. 129–157.

Siegel, R.A., 1993. Hydrophobic weak polyelectrolyte gels: Studies of swelling equilibria and kinetics. In: Dusek, K. (Ed.), Responsive Gels, Transitions Vol. I. Springer-Verlag, Berlin Heidelberg, pp. 233–267.

Thomas, J.E., 1941. An improved cannula for gastric and intestinal fistula. Proc. Soc. Exp. Biol. Med. 46, 260–261.

Verdugo, P., 1984. Hydration kinetic of exocytosed mucins in cultured secretory cells of the rabbit trachea: a new model. In: Jonathan, N., O'Connor, M. (Eds.), Mucus and mucosa, Ciba Foundation Symposium 109. Pitman, London, pp. 212–225.

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