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GI TRANSIT OF POTENTIAL BIOADHESIVE SYSTEMS IN THE RAT

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The oral availability of a drug may be limited by the residence time of the dose in the upper GI tract. Among the methods proposed to delay the transit of oral pharmaceutical formulations is the use of bioadhesion. The GI transit of four potential bioadhesive polymers, presented in a number of different formulations, was investigated in the rat. Formulations were dosed orally, and GI transit was assessed by killing animals at various intervals and sectioning the GI tract. Significant differences in oro-caecal transit were obtained with certain formulations, with 4% and 5% solutions of Carbopol 934 showing delays of 25% in transit to the ileo-caecal junction.

INTRODUCTION

It is known that the oral availability of certain drugs may be limited by GI residence time, and it has been postulated that the availability of these drugs may be increased by delaying the GI transit of the dose. In an earlier publication, Harris et al. [1] discussed the subject of delayed-transit formulations and investigated the GI transit of some potential bioadhesive formulations in man. This paper extends the work in a second species, the rat, using a different experimental technique. It examines the transit characteristics of some similar formulations in more detail, as well as looking at some additional polymers.

MATERIALS AND METHODS

Materials

The materials used were as follows: polycarbophil — BF Goodrich, U.K.; Carbopol 934 (mol.wt. = 3×10^6) — BF Goodrich, U.K.; poly(styrenesulphonic acid) (Versa-TL 600, mol.wt. = 6×10^6) — National Starch and Chemical Co., U.S.A.; hyaluronic acid (mol.wt. = ca. 2×10^6) — ICI Pharmaceuticals, U.K.; hydroxyethyl cellulose (Natrosol-250HHX, mol.wt. = 10^6) — Hercules Inc., U.S.A.; lactose (Serolac) — Dairy Crest, U.K.; size 9 hard gelatin capsules — Elanco Qualicaps, U.K.; chromium-51-labelled microspheres (Nen-trac) – DuPont GmbH, W. Germany.

Polycarbophil and Carbopol 934 have been proposed as bioadhesives by a number of workers [2–5]. Poly(styrenesulphonic acid) (PSSA) was included in the study as it has been suggested that sulphonated polymers have higher binding affinities to proteins than carboxylated materials [6]. The mucopolysaccharide hyaluronic acid (HA) has been shown by Gurny and co-workers [7] to interact with the corneal tissue, so prolonging precorneal residence time: concentrations of 0.0625 to 0.75% were shown to be most effective. The material has the drawback of being expensive. The control used was

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hydroxyethyl cellulose (HEC): this material has been used as a control in GI transit studies in the dog, as it forms viscous solutions with no calorific content [8].

PSSA, HA and HEC are water soluble, and were used in these investigations as aqueous solutions. Polycarbophil and Carbopol existed as dispersions at acid pH: at neutral pH, polycarbophil formed a viscous gel and Carbopol a solution. Polycarbophil, Carbopol, PSSA and HEC all have LD_{50}s of 1 g/kg or greater; details of the acute oral toxicity of HA were not available.

The mean particle size of the lactose was determined, by optical microscopy, to be 11 μm. The size 9 hard gelatin capsules used were 8.5 mm in length and 2.3 mm in diameter, with a capacity of approximately 29 μl. The ^{51}Cr-labelled microspheres consisted of a polymeric core, containing ^{51}Cr, coated with a polymeric resin. These were 16.5 ± 0.1 μm in size, with a density of 1.4 g/cm^3. They were obtained as a suspension in 0.9% sodium chloride solution, at a specific activity of 500 μCi/ml.

Rheological studies

It has previously been shown [9] that the viscosity of polymer solutions can affect their GI transit. These studies were carried out using aqueous solutions and suspensions of the material on a Contraves Rheomat 135 (Contraves AG, Switzerland) interfaced with a Hewlett Packard 85B microcomputer (Hewlett Packard Co., U.S.A.). The shear stress was measured over a range of shear rates, the apparent viscosity at each shear rate was calculated, and the viscosity at one specified shear rate was taken as a measure of the viscosity of the system. Studies were carried out at 37°C.

Preparation of formulations

A total of 12 different formulations were investigated, 2 of which were studied in duplicate. The compositions of the various formulations investigated, and the doses administered, are shown in Table 1.

The polymer solutions or suspensions were prepared by gradual addition of an appropriate quantity of the polymer to distilled water with constant stirring. All aqueous formulations were prepared 18 hours prior to dosing, to allow the polymer to hydrate fully and to allow trapped air bubbles to clear. Shortly before dosing, 0.1 ml of the ^{51}Cr-labelled microsphere suspension was added to 9.9 ml of the polymer system, and the product thoroughly mixed by inversion and stirring.

For the preparation of the dry formulation, 50 μl of the ^{51}Cr-labelled microsphere suspension was transferred to a glass vial and dried at 40°C under a stream of nitrogen. 250 mg lactose was added, the system was mixed by spatula, and 250 mg Carbopol was added gradually with constant mixing. 10 mg quantities of the powder mix were accurately weighed into the capsules, corresponding to 5 mg doses of Carbopol. Lactose was added to increase the rate of

TABLE 1

Compositions of bioadhesive and control formulations investigated in the rat

Study	Formulation	Administration	Dose given
1	7.5% Polycarb	gavage	50 μl
2	0.2% Carbopol	gavage	50 μl
3	4.0% Carbopol	gavage	50 μl
4	5.0% Carbopol	gavage	50 μl
5	6.0% Carbopol	gavage	50 μl
6	10.0% PSSA	gavage	50 μl
7	1.0% HA	gavage	50 μl
8	1.5% HEC	gavage	50 μl
9	1.5% HEC	capsule	22 μl
10	7.5% HEC	capsule	22 μl
11	5.0% Carbopol	capsule	22 μl
12	5 mg Carbopol and 5 mg lactose	capsule	10 mg

hydration of the Carbopol and to aid in the handling of the material which is fine and electrostatic in its pure state.

GI transit studies

The GI transit of these labelled formulations was determined by the method of Varga [10]. Twenty male rats (Wistar-derived A.P. strain) were used for each formulation. They were fasted for 18 hours prior to the study and for the duration of the study, but were allowed free access to water throughout. On the morning of the study, each animal was dosed orally with the formulation under investigation. A quantity of the suspension was transferred to a 2.5 ml gastight glass syringe (Hamilton Bonaduz AG, Switzerland), fitted with a mechanical syringe driver (Hamilton Co., U.S.A.), and either a 100 mm long round-tipped steel needle or a flexible plastic catheter (8-gauge infant feeding tube, Portex, U.K.). The gavage tube was passed down the oesophagus and into the stomach of the conscious rat and the syringe driver was activated, delivering a 50 μl dose of suspension directly into the stomach. Where the formulation was too viscous to be dosed by gavage, the suspension was filled into gelatin capsules, using a wide-bore needle, immediately prior to administration. When filled in this way, these capsules held 21.7 ± 0.6 mg polymer suspension, and this dose was considered to be sufficiently precise for these studies. (Being thin-walled, the gelatin capsules rapidly absorbed water from the dosing suspensions and only remained hard enough to handle and administer for around 20 seconds after filling.) The capsules were administered directly into the stomach, of the rat by means of an applicator supplied by Elanco, U.K.

At each of 5 time points up to 7 hours after dosing, 4 rats were killed and the distribution of the formulation along the GI tract was determined. The time points used were $\frac{1}{2}$, 2, $3\frac{1}{2}$, 5 and 7 hours after dosing. The animals were killed by carbon dioxide asphyxia. The abdomen was opened along the midline and the various organs of the GI tract located. The stomach, duodenum, caecum and colon were ligated and excised. The ligament of Treitz was taken to be the junction between the duodenum and jejunum. The remainder of the small intestine was removed, separated from its mesentery, measured into 4 equal lengths and these sections ligated and cut. The 8 segments were placed in plastic sample tubes for counting on an automatic gamma counter (LKB Wallac 1280 Ultrogamma, LKB-Produkter AB, Sweden).

Analysis of results

The object of this analysis was to determine transit times for each of the formulations through various regions of the GI tract, and to find whether any formulation differed significantly from the others. The analysis of the results was complicated by the fact that each rat was used once only, i.e. each of the 4 data points at each of the 5 time points represented a different animal.

The counts measured for each segment were corrected for background activity. The activity recovered from each animal was totalled and normalised to 100%. This gave a segment-by-segment percentage distribution of activity along the GI tract in each animal. The mean distribution along the GI tract at each time point was calculated from the distributions in the 4 animals at that time point. The change in this distribution with time was thus followed.

By collecting data for 8 different segments of the GI tract, it would have been possible, in principle, to calculate transit times for each of these segments. In practice, however, the variability seen in the data meant that this analysis would have provided little additional information. Furthermore, transit times could not be calculated for regions distal to the ileo-caecal junction (i.e. the caecum or colon) since most of the radiolabel was still present in or upstream of the caecum at the end of the experiment. The data for these individual segments

were therefore grouped to give activity–time data for 3 regions of the GI tract:

a. segment 1 — percentage activity remaining in the stomach, against time;
b. summation of segments 1–4 — percentage activity in or upstream of segment 4 (a point midway between the proximal jejunum and distal ileum), against time;
c. summation of segments 1–6 — percentage activity in or upstream of segment 6 (the ileocaecal junction), against time.

To obtain numerical estimates of transit times, two empirical mathematical models were fitted to the data. Model 1 was a sigmoid, as it has been shown by Varga [10] that the transit profiles obtained are approximately sigmoid in shape. Considering a radio-labelled marker, dispersed along a discrete length of the GI tract and moving at a constant velocity past a fixed point, the percentage of marker upstream of this point could be expected to show a sigmoid relationship with time. The function fitted took the form:

$$y = 100 - \left[\frac{100}{1 + e^{S(\log T - H)/25}} \right] \quad (1)$$

where y = percentage remaining upstream of that point, T = time, S = parameter relating to the slope of the curve, and $H = \log T$, at the point where $y = 50\%$. Two additional parameters were ascribed values of 100, since it was reasonable to expect the upper and lower limits of the curve to be 100% and 0%, respectively.

Parameter S described the slope of the sigmoid, which may be considered a measure of the linear distribution of the label within the GI tract. Parameter H was the log of the $T_{50\%}$ emptying time of the formulation from the segment in question. This model was fitted to the GI transit data for each formulation, using the individual data from all 20 rats. It was fitted to the three data sets — segment 1, the summation of segments 1–4, and the summation of segments 1–6.

Model 2 was a mono-exponential: this is the model which is generally considered to best represent the process of stomach emptying. The function fitted took the form:

$$y = Ce^{-KT} \quad (2)$$

where T=time, C=y-intercept, and k=exponential rate constant.

Parameter C defined the y-intercept of the curve: this parameter could be expected to be common to all formulations, at around 100%, provided they showed approximately exponential emptying patterns without pronounced "lag" or "dump" phases. Parameter K, the exponential rate constant, defined the slope of the curve. The $T_{50\%}$ emptying time from the segment in question could be calculated from the relationship:

$$T_{50\%} = \frac{0.6931}{K} \quad (3)$$

This model was fitted to the individual segment 1 (stomach emptying) data of all 20 rats, for each formulation.

The models were fitted to the data by a process of non-linear least-squares iteration (Marquardt method). All fitting and analysis was done using the SAS software package (SAS Institute Inc., U.S.A.). For each mathematical model, a number of statistical fits were made, beginning with the full model (14 separate $T_{50\%}$ times and slope/intercept parameters), reducing initially to a common slope/intercept and different $T_{50\%}$ times, and reducing eventually to single common slope/intercept parameters and $T_{50\%}$ times (i.e. where all the formulations would be statistically indistinguishable). Statistical differences were tested for by comparing the residual sum of squares (RSS) of each reduced fit with that of the full fit, using an F-test (eqns. 4 and 5).

$$\mathrm{RMS_d} = \frac{\mathrm{RSS_2} - \mathrm{RSS_1}}{{}^{\circ}f_2 - {}^{\circ}f_1} \quad (4)$$

and

$$F_{(^{\circ}f_d,^{\circ}f_1)} = \frac{RMS_d}{RMS_1} \quad (5)$$

where RMS_d = residual mean square of difference between the fits, RMS_1 = residual mean square of first fit, RSS_1 and RSS_2 = residual sums of squares of the two fits, $^{\circ}f_1$ and $^{\circ}f_2$ = degrees of freedom of the two fits, and $^{\circ}f_d = {}^{\circ}f_2 - {}^{\circ}f_1$.

Critical values of F for these degrees of freedom were obtained from tabulated values of the upper 5% points of the F-distribution.

Each reduction in the number of parameters (i.e. each successive grouping of formulations) gave an increase in the residual sum of squares (RSS) of the fit. At some point, further increase in the RSS generally became statistically significant, and this point represented the furthest permissible reduction of the model. Differences in $T_{50\%}$ values between formulations with common estimates for the slope/intercept parameter therefore indicated significantly different transit times for the segment in question.

RESULTS AND DISCUSSION

Rheological studies

For the purpose of these investigations, the viscosity at one rate of shear — 2 second^{-1} — was taken as a measure of the viscosity of the system. This approximation was judged to be valid, as all the systems investigated exhibited similar pseudoplastic flow and (with the exception of polycarbophil and Carbopol at low pH) were aqueous solutions of polymers.

It was not possible to determine accurately the viscosities of higher concentrations of PSSA, since the sample exhibited "plug flow" — i.e. shear occurred at the interface between the sample and the bob. Furthermore, rheological studies were not performed on the sample of HA, since this material was not available in sufficient quantity. Concentrations of these materials showing similar consistencies to the other three materials at the appropriate pH values were therefore estimated.

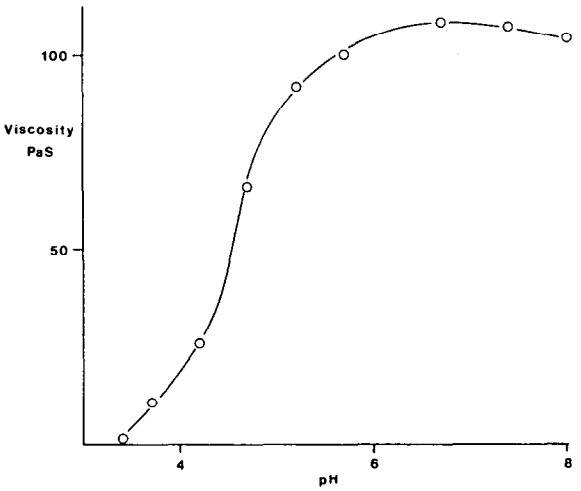


Fig. 1. Viscosity–pH profile for 1% Carbopol 934, at a shear rate of 2 s^{-1}.

All four materials investigated exhibited pseudoplastic flow, characteristic of polymers in solution, with no significant hysteresis. The poly(acrylic acids) showed pronounced changes in viscosity with pH (Fig. 1). This effect was related to the ionisation and swelling of the polymer around the pK_a of acrylic acid. This change in viscosity with pH was significant in relation to GI transit studies, since these materials were dosed into the stomach, a region of low pH, and then emptied into the small intestine, where the pH approaches neutrality. The poly(acrylic acids) also showed decreases in viscosity with increasing electrolyte concentration. The other two polymers, PSSA and HEC, showed viscosities independent of pH and electrolyte concentration.

From these studies, it was possible to estimate the viscosities of various concentrations of the four polymers at various pHs. The following four systems showed approximately equal viscosities at pH 3–4: 7.5% polycarbophil; 5% Carbopol; 10% PSSA; 1.5% HEC; 1% HA. At neutral pH, the above concentration of HEC (1.5%) was approximately iso-viscous with

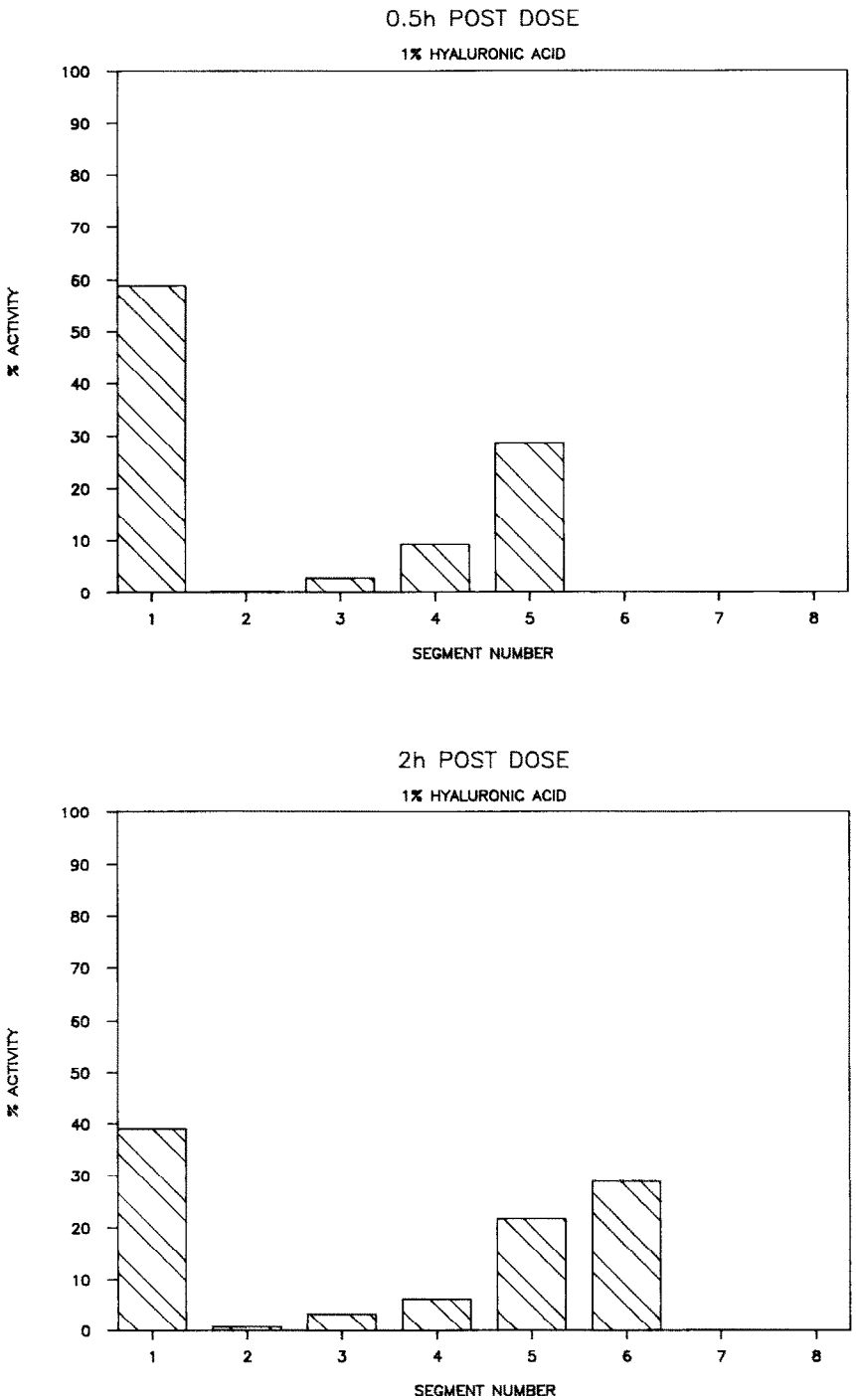
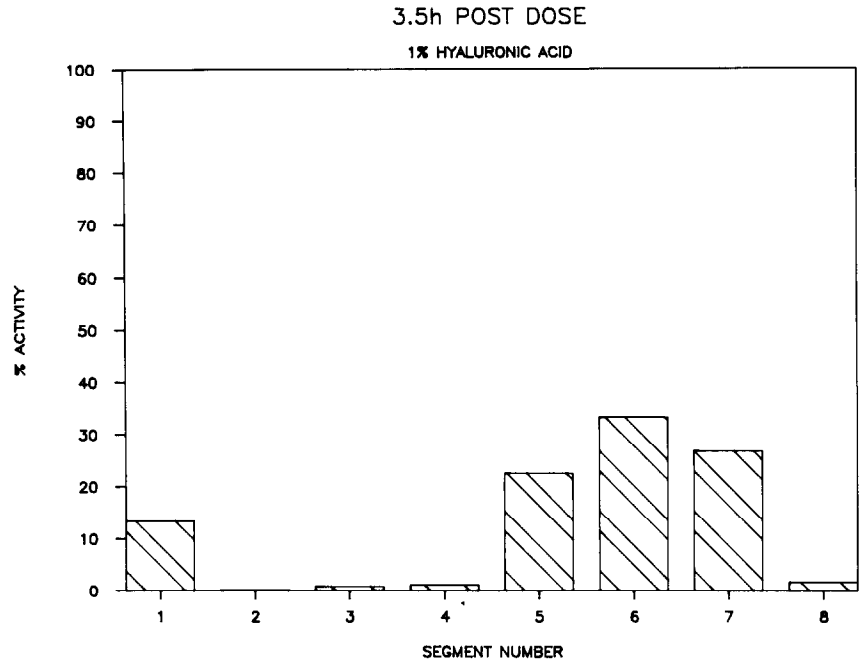


Fig. 2. Distribution of one formulation (1% hyaluronic acid) along the GI tract at 0.5 and 2 h post dose (seg 1 = stomach, seg 2 = duodenum, segs 3–6 = small intestine, seg 7 = caecum, and seg 8 = large intestine).



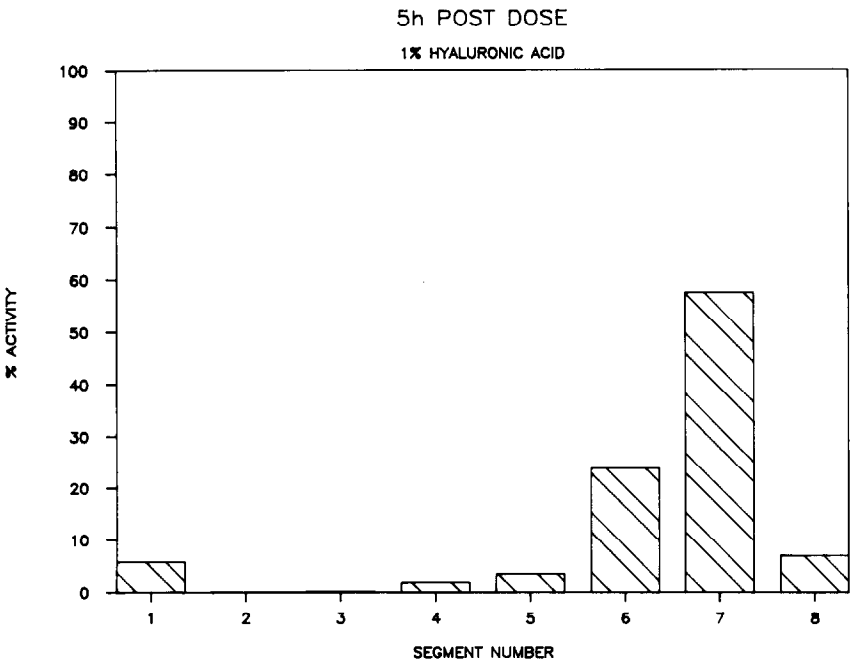


Fig. 2. Cont. Distribution at 3.5 and 5 h post dose.

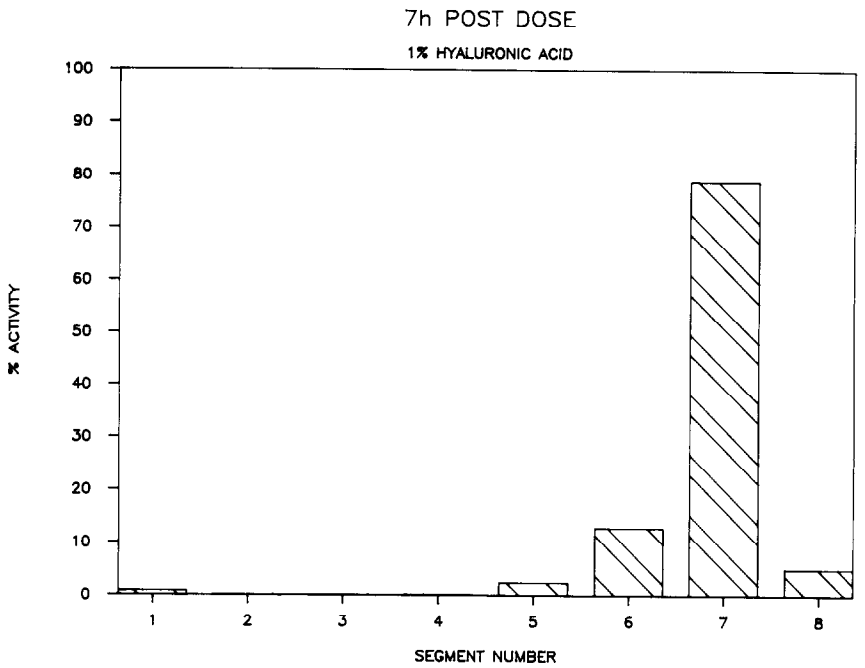


Fig. 2. Cont. Distribution of one formulation (1% hyaluronic acid) along the GI tract at 7 h post dose (seg 1 = stomach, seg 2 = duodenum, segs 3-6 = small intestine, seg 7 = caecum, and seg 8 = large intestine).

0.2% Carbopol, while the above concentration of Carbopol (5%) was approximately iso-viscous with 7.5% HEC.

These correlations were used as a basis for selecting the concentrations of the various materials dosed to rats in the GI transit studies (see Table 1).

GI transit studies

The total activity recovered from each rat was calculated and the mean and SD of these totals were determined for each formulation. The coefficient of variance was generally below 20%, indicating reasonably precise dosing given the viscous nature of the gels and the small volumes administered.

To illustrate the results obtained, Fig. 2 shows the distribution of labelled polymer through the various segments of the GI tract at each time point for a typical formulation (1% HA).

Table 2 shows the $T_{50\%}$ transit times obtained by fitting the mathematical models to the three data sets (segments 1, 1–4 and 1–6). These values represent transit times from dosing to the distal ends of these regions. These $T_{50\%}$ values were derived from the parameter estimates representing the best fit attainable in each case, as judged by the minimum value of the residual mean square of the fit.

The stomach emptying patterns of the 12 formulations (segment 1 data) were not adequately described by just one model. Certain of the formulations (e.g. formulations 2, 6, 7 and 9) appeared to empty rapidly, starting shortly after dosing: this emptying pattern was thought best fitted by the exponential model. Certain other formulations (e.g. formulations 1, 3, 4 and 5b) appeared to empty only after a "lag" period had elapsed: this emptying pattern appeared better fitted by the sigmoid model, where higher estimates of the H parameter were obtained, thus accommodating the lag phase. Little useful information could be obtained from at-

TABLE 2

$T_{50\%}$ transit times calculated for the stomach and the upper and lower small intestine (times in minutes)

Formulation		Seg 1 (stomach)	Seg 1–4 (upper sml int.)	Seg 1–6 (lower sml int.)
1	7.5% Polycarb	193[b]	207	341
2	0.2% Carbopol	61	110	310
3	4.0% Carbopol	193[b]	207	390
4	5.0% Carbopol	193[b]	207	390
5a	6.0% Carbopol	89	141	310
5b	6.0% Carbopol	171[b]	207	310
6	10.0% PSSA	89	110	257
7	1.0% HA	89	110	257
8	1.5% HEC	89	141	310
9	1.5% HEC[a]	61	110	310
10	7.5% HEC[a]	119	141	310
11	5.0% Carbopol[a]	89	141	257
12a	5 mg Carbopol and 5 mg lactose[b]	235[b]	244	310
12b	5 mg Carbopol and 5 mg lactose[b]	119	141	310
Mean		128	158	312
Standard error		15	13	11

[a]Formulations dosed in capsules.
[b]Formulations fitted by sigmoid model.

tempting to fit one model to all studies: given the heterogeneity of these studies, neither fit would satisfactorily reduce to a small number of common parameters. The 14 studies were therefore divided into two groups, one of which was modelled by the exponential function and the other by the sigmoid function. The $T_{50\%}$ transit times calculated for segment 1 ranged from 61 to 119 minutes for the exponential group and from 171 to 235 minutes for the sigmoid group, as shown in Table 2. It was considered that this treatment gave a better overall representation of the data. No significant differences could be determined within either the sigmoid or exponential groups, and comparison could not be made between these two models. It should be noted, however, that the formulations fitted by the sigmoid model (1, 3, 4, 5b and 12a) gave consistently longer $T_{50\%}$ transit times than the exponential group.

The second column of Table 2 shows the $T_{50\%}$ estimates from dosing to the distal end of segment 4, a point mid-way along the small intestine. With the exception of formulation 12a, for which the data were highly variable at certain time points, all formulations could be fitted by a common slope. These formulations were best represented, as shown, by 3 $T_{50\%}$ values. The longest transit times were shown by formulations 1, 3, 4 and 5b, and these differed significantly from the remaining formulations. Formulation 12a also showed a long $T_{50\%}$ transit time to this point, but statistical comparison of transit times was not possible as a common slope could not be fitted to this and the other formulations.

$T_{50\%}$ transit times from dosing to the distal end of segment 6 (the ileo-caecal junction) are shown in the third column of Table 2. The 12 formulations were best represented by 4 curves, described by a common slope and 4 $T_{50\%}$ values. Significant differences existed between three groupings of formulations, comprising: (a) 3 and 4 — 4% and 5% Carbopol, long $T_{50\%}$; (b) 6 — 10% PSSA, short $T_{50\%}$; (c) the remaining 11 formulations, intermediate $T_{50\%}$.

The differences between the transit times determined for these three regions of the GI tract represent transit times through segments 2–4 and segments 5–6 (the upper and lower small intestine). These figures show that transit through the duodenum and upper small intestine was rapid (31 ± 5 minutes): transit through the lower small intestine was slower (154 ± 10 minutes), and was less variable than through the other two regions studied. These transit times illustrate the gradual decrease in propulsion which is seen in moving distally through the small intestine: a similar effect has been observed in man [12]. The mean transit time through the whole small intestine was 184 ± 12 minutes. These results may be compared with the transit times of a number of potentially adhesive formulations in man [1]: comparison shows longer gastric emptying times in rat than in man (128 ± 15, cf. 42 ± 10 minutes) but sim-

ilar small intestinal transit times (184 ± 12, cf. 140 ± 7) in the two species.

Overall, these results show that the $T_{50\%}$ values for the stomach were more variable than those for the small intestine. There are two possible causes of this variability. Firstly, the process of gastric emptying in the fasted state is governed by the interdigestive myoelectric complex (IMC), a cyclical pattern of contractile activity [12]. Thus the residence time of a formulation in the fasted stomach may depend, to a large extent, on the point in the cycle at which the formulation is dosed. Gupta and Robinson [13] showed that a bolus of around 100–150 ml of water was necessary to break the cycle of the IMC in the dog; the doses administered here were probably too small to affect the IMC, even given the access of the rats to drinking water. Secondly, the gastric emptying of certain of the formulations may have been delayed by formulation-related effects, such as their bioadhesive, viscous or swelling properties. In particular, it is probable that some of the longer $T_{50\%}$ values represented significant formulation-related differences in transit.

Of the agents investigated, the acrylic acid derivatives, polycarbophil and Carbopol, were the most likely to be of use in delaying GI transit. 7.5% polycarbophil showed a delay in transit to the ileo-caecal junction, although this effect was not significant. 4% and 5% Carbopol showed statistically significant delays of around 25% in transit to the ileo-caecal junction. Interestingly, 6% Carbopol did not show the same effects on transit. The reason for this is not known; it may be that 6% Carbopol provided sufficient bulk or viscosity to break the IMC and trigger the fed motility pattern. 10% PSSA and 1% HA — the other two potential bioadhesives — showed normal transit through the stomach and small intestine. Formulations showing delays in transit at segment 6 also showed delays of similar magnitudes at segments 1 and 4. It seems likely therefore that the observed delays in transit to the ileo-caecal junction were due to delays in the gastric emptying of these formulations.

Two possible causes of these delays are the viscosity of the formulation and adhesion of the polymer to the mucus layer of the GI tract. An attempt was made to discriminate between these two effects by dosing suspensions of Carbopol and HEC of various concentrations. Interpretation of the results was difficult, however, given the changes in viscosity of the Carbopol suspensions in passing from the stomach, a region of low pH, into the small intestine, at pH 6–7. It was impossible to estimate the likely rates of neutralisation, hydration and swelling of the polymer in the GI tract, and the extents to which these would affect the volume or the viscosity of the suspension. Practical difficulties were also encountered in dosing formulations of particularly high or low viscosity.

Formulations 9 and 11 were administered to determine whether the differences seen between Carbopol and the HEC control when dosed by gavage could be reproduced when dosed in capsules. The results showed these two formulations to have similar transit times. This suggested either that dosing by capsule altered the transit of the formulation, such as by invoking the fed motility pattern in the stomach, or that the smaller dose administered was insufficient to affect transit. 0.2% Carbopol (formulation 2) was dosed since it showed a similar viscosity to the control at pH 5 and above; 7.5% HEC in capsules (formulation 10) was dosed since it had a similar viscosity to 5% Carbopol at neutral pH. Both of these formulations showed similar transit times to the control values.

In the light of these results, it was not possible to say conclusively from the capsule-dosed formulations that viscosity did not affect transit. The fact that the delays in transit appeared to originate in the stomach, however (a region of low pH), suggested that viscosity was not a major factor: all five polymers investigated were dosed as suspensions of approxi-

mately equal viscosities at acid pH (formulations 1, 4, 6, 7 and 8), and only two of these formulations showed delays in transit.

The dry formulation of Carbopol, which was similar to one of the formulations investigated in man [1], showed little effect on GI transit: one study showed delayed gastric emptying, but no significant differences were observed. Investigation of a dry dosage form introduced a number of complicating effects: although the dose of Carbopol administered was larger than that given in suspension, the effective dose would depend on the rate and extent of hydration of the powder plug in the GI tract. These observations, along with the results of Harris et al. [1], may reflect the importance of polymer hydration in bioadhesion.

CONCLUSIONS

In conclusion, it was observed that two of the formulations investigated — 4% and 5% Carbopol — showed significant delays in oro-caecal transit — delays of approximately 25% over the usual range of transit times. It seems likely that these delays were due to a form of bioadhesive interaction, although these studies provided no indication as to the mechanisms involved. It was considered that these observed differences could provide a basis for a delayed-transit formulation, in order to increase the oral availability of a poorly absorbed drug.

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