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GI TRANSIT OF POTENTIAL BIOADHESIVE FORMULATIONS IN MAN: A SCINTIGRAPHIC STUDY

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It is known that the oral availability of certain drugs can 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. In this work, the gastric emptying and small intestinal transit of some potentially adhesive formulations were studied in man by gamma scintigraphy. Two different capsule formulations were investigated, in combination with two potentially bioadhesive polymers and a non-adhesive control. Small differences in oro-caecal transit were seen with certain combinations, but no dramatic effects on GI transit were observed.

INTRODUCTION

The gastro-intestinal (GI) transit characteristics of a broad range of oral pharmaceutical formulations have been studied by a number of techniques, in particular by gamma scintigraphy. Davis and co-workers [1] reported the results of a large number of such scintigraphic studies: they showed gastric emptying times of generally under 2 hours for pellets and non-disintegrating units in the fasted state, and of up to 4 hours or more in the fed state. The small intestinal transit time was generally in the range 2–6 hours, irrespective of the fed or fasted state. These results thus indicated a residence time in or above the small intestine of around 4–8 hours.

It is known that, in certain situations, the oral availability of a drug may be limited by the GI transit time of the dose [2]. Firstly, a number of drugs are absorbed only from the small intestine, and then only slowly, with the result that their availability is limited by the residence time of the dose in or upstream of the small intestine. Where the bioavailability of the drug is related to the GI transit time, there is the risk of variable and unpredictable availability. Secondly, the absorption, and possibly the release, of drug from a controlled-release formulation may depend in part on the location of the system within the GI tract. In the case of drugs which are absorbed only from the small intestine, release times greater than 4–8 hours are likely to be ineffective. In any case, release times in excess of 24–48 hours are precluded, since the system is likely to have been voided from the GI tract altogether by this time.

It has been shown that the concomitant intake of food can delay the gastric emptying of the dose, extending the time available for absorption and increasing the fraction of the dose

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absorbed [3,4]. Similarly, the co-administration of propantheline, a drug which shows gastric emptying and small intestinal transit, has been shown to increase the availability of a number of drugs [5,6].

Several techniques have been proposed to modify the GI transit of oral pharmaceutical formulations. Examples include formulations which swell or expand in the gastric content and are retained in the stomach by floating on the gastric content or by being too large to pass through the pylorus [7–11]. Another approach is to design a formulation which can adhere to the lining of the stomach or small intestine, thus retaining the dose in the upper GI tract. This utilises the phenomenon of bioadhesion — an adhesive interaction between a polymeric material and a biological surface. The concept of bioadhesion, some proposed mechanisms for the interaction, and some of the *in vitro* and *in vivo* systems used to study bioadhesion have been described elsewhere in the literature [12–16]. In particular, Robinson and co-workers [17,18] investigated capsule formulations containing a proposed bioadhesive, polycarbophil, in the rat: they demonstrated that these formulations showed delayed GI transit and gave improved availability of a poorly absorbed drug, chlorothiazide. The aim of this study was therefore to evaluate a number of similar and potentially bioadhesive formulations in man, using the technique of gamma scintigraphy.

MATERIALS AND METHODS

Materials

The materials used were as follows: Amberlite IRA-410 ion exchange resin — BDH Chemicals, U.K.; polycarbophil — BF Goodrich, U.K.; Carbopol 934P — ICI Pharma, France; Lactose BP (Serolac) — Dairy Crest, U.K.; size 0 hard gelatin capsules — Elanco Qualicaps, U.K.; sodium ^{99m}pertechnetate solution — Amertec II generator, Amersham International, U.K.

Amberlite IRA-410 is a strongly basic anion exchange resin, which has previously been shown to be a good marker for scintigraphic studies of this kind [19], since it is inert and binds the radiolabel irreversibly. The resin was fractionated by sieving and the fraction 710–1000 μm was retained. A quantity of the resin was milled using a fluid jet mill (Gem-T research model, Helme Products, U.S.A.), operated by nitrogen gas at a pressure of 100 psi. The product was fractionated by sieving and the fraction 5–50 μm was retained: the mean particle size of this fraction was determined by optical microscopy to be 20 μm.

Polycarbophil and Carbopol are polymers of acrylic acid, differing in the extent of cross-linking and in the cross-linking agent used. Polycarbophil is cross-linked with divinyl glycol and is insoluble in water, while Carbopol is cross-linked with allyl sucrose and is water-soluble. Both are licensed for human use, and have LD_{50}s of around 4 g/kg in rat.

The mean particle size of the lactose was determined by optical microscopy to be 100 μm, with a range of 40–150 μm.

Preparation of formulations

The two formulations investigated were similar to those studied by Longer and co-workers [18]. Both of these formulations consisted of 100 mg Amberlite resin, labelled with 50 μCi ^{99m}Tc, and 250 mg bioadhesive or non-adhesive diluent, contained in a size 0 hard gelatin capsule. Formulation 1 contained radiolabelled ion exchange resin beads, 710–1000 μm, comparable in size to the beads found in many sustained-release formulations. Formulation 2 contained radiolabelled resin of a smaller particle size (20 μm), with the same adhesive and non-adhesive diluents: this presented a more intimate mix of resin and diluent, and was thus more representative of a capsule formulation containing a fine powder mix. For each of the two formulations, two bioadhesive forms were compared with a control form, in which the ad-

hesive was replaced with an equal weight of lactose. Lactose dissolves readily in the GI fluids and would be expected to disperse rapidly, exerting no effect on the GI transit of the labelled beads.

The Amberlite resin was radiolabelled with technetium-99m by the procedure described previously [20]. *In vitro* studies were carried out to confirm that the radiolabel remained bound to the resin for the duration of the study. Measured amounts of radiolabelled resin were incubated at 37 °C in isotonic aqueous media. The pH was held at 2.0 for a hour and was then raised to 7.0 for a further 3 hours. At the end of this time, the activity remaining associated with the resin was measured, corrected for decay, and expressed as a percentage of the initial activity.

In vitro disintegration studies

To determine the likely behaviour of these formulations in the GI tract, *in vitro* disintegration studies were performed, using the disintegration apparatus described in the British Pharmacopoeia [21]. The formulations tested were as described above, except that they were not labelled with ^{99m}Tc. The disintegration media used were buffered aqueous solutions, of pHs from 2.0 to 8.0, made isotonic by the addition of sodium chloride. All disintegration studies were carried out at 37 °C, and 6 capsules were used for each determination. The disintegration time was considered to be the time taken for all of the contents of the capsule to pass through the mesh of the disintegration tube: where a formulation was not fully disintegrated after 200 minutes, the remaining undisintegrated material was removed from the tube, dried, weighed and expressed as a percentage of the original capsule content.

Gamma scintigraphy

The gamma camera used for these studies was a Scinticamera NE 8960 (Nuclear Enterprises, U.K.) with a 40 cm field of view and fitted with a low-energy parallel-hole collimator. It was linked to an on-line computer system (MAPS 2000, Link Systems, U.K.) for acquisition and storage of data. This system gave a resolution of approximately 2 cm (i.e. it was able to resolve two discrete regions of activity, separated by this distance). The study was approved by the University ethical committee, and the administration of radioisotopes to human volunteers was carried out under a licence from the Department of Health. An individual undergoing 3 such investigations was exposed to a whole-body radiation dose of 2.9 mrem, which is around 1% of the usual annual exposure from natural sources.

Male volunteers participated in these studies, and all had given their informed consent. Formulation 1 was studied in 8 volunteers, of mean age 28 years (range 19–44) and mean weight 67 kg (range 59–75 kg). Formulation 2 was studied in 6 volunteers, of mean age 29 years (range 24–46) and mean weight 66 kg (range 62–74 kg). For each formulation, each subject received each of the three forms (polycarbophil, Carbopol and control) once only, on three separate occasions, and in a randomised fashion.

The subjects fasted for 12 hours prior to the study, to minimise the effects of food on GI motility. On the morning of the study, the subject swallowed a capsule followed by 50 ml cold water. This volume was considered sufficient to ensure that the capsule passed directly into the stomach, without unduly affecting gastric motility. The subject then lay in a supine position under the gamma camera for imaging. The subject was imaged continuously for the first 60 minutes, or until the formulation was seen to empty from the stomach (whichever was the earlier). Images of 60 seconds duration were collected continuously over this period. Where the formulation had not emptied from the

stomach after 60 minutes, imaging was continued intermittently. Single 60-second images were collected, initially at 10–15 minute intervals and later at 30 or 60 minute intervals, until the formulation had left the stomach. The subject was permitted to get up and move around, and was repositioned under the camera for each image. No food or drink were permitted until the formulation had fully emptied from the stomach. The appearance of the formulation in the ascending colon was recorded by imaging at intervals, commencing when the formulation emptied from the stomach. These images were collected at approximately 30–60 minute intervals and were of 60 or 120 seconds duration.

To allow successive images to be correctly aligned relative to one another, radiolabelled markers were taped to either side of the body at around the level of the 5th lumbar vertebra for the duration of the study. At the end of the study, the images were aligned on the screen using these markers as reference points.

Two events were thus recorded scintigraphically; the emptying of the formulation from the stomach and its appearance in the ascending colon, as described by Christensen and coworkers [22]. The anatomical position and shape of the stomach are such that the stomach region could be readily identified from a sequence of scintigraphic images. A "region of interest" was drawn around the stomach and the activity within this region was calculated for each image. These counts were corrected for isotopic decay and plotted against time. From this plot, the $T_{50\%}$ and $T_{90\%}$ — the time taken for 50% or 90% of the activity to leave the stomach — was determined. Similarly, the anatomical position and shape of the ascending colon allowed it to be readily identified from the later images. A "region of interest" was drawn around the colon and a second activity–time plot was constructed: from this plot, the $T_{50\%}$ and $T_{90\%}$ at the colon was determined. The difference between the T values for gastric emptying and colon arrival were taken to be the small intestinal transit time of the formulation.

RESULTS AND DISCUSSION

Labelling efficiency

The *in vitro* labelling studies showed that $99 \pm 1\%$ of the ^{99m}Tc label remained bound to the resin after incubation for four hours at 37°C in isotonic media at pHs of 2.0 and 7.0. These results confirmed that ^{99m}Tc-labelled Amberlite IRA-410 resin was a good marker for GI transit studies of this kind.

In vitro disintegration studies

The results of the *in vitro* disintegration studies showed marked differences between the three excipients investigated.

Disintegration times for the control, lactose, were consistent at around 2 minutes for both formulations 1 and 2. Lactose, being hydrophilic and water soluble, allowed rapid wetting of the system and dispersion of the Amberlite resin. The main determinant of disintegration time here was probably the dissolution of the shell of the hard gelatin capsule.

Polycarbophil gave mean disintegration times of between 18 and 37 minutes for formulation 1, and between 9 and 77 minutes for formulation 2. These times were markedly longer than those seen with lactose, indicating that polycarbophil slowed the dispersion of the resin. No overall differences between the two formulations were apparent, and these effects appeared to be independent of pH.

Carbopol gave slower disintegration still: in almost all determinations, the formulation had not fully disintegrated after 200 minutes. The disintegration of formulation 1 appeared to be related to pH, with around 10% remaining after 20 minutes at pH 2–4 compared with 80–90% at pH 6–7. Formulation 2 disintegrated slightly more rapidly, and apparently independently of pH.

These results indicated that the two bioadhesives, polycarbophil and Carbopol, considerably slowed the disintegration and dispersion of

the resin components of these capsule formulations. Since the agitation conditions generated by the B.P. disintegration apparatus were probably more vigorous than those encountered in the GI tract, the *in vivo* disintegration of these formulations was likely to be slower still. One consequence of this was that the formulations would probably have been present as agglomerates rather than uniform dispersions of resin for a substantial part of their residence time in the upper GI tract, and would have been handled as such by the GI tract.

Gamma scintigraphy

Figure 1 illustrates one complete data set, showing the gastric emptying and arrival at the colon for one such formulation.

It may be argued that the radiolabelled resin may have separated from the bioadhesive polymers in the GI tract, and that the transit times determined reflected the transit of the resin alone rather than that of the whole formulation. The results of the disintegration studies on these formulations suggest that this was probably not the case. The lengthy disintegration times seen, even under the vigorous agitation conditions employed, indicated that the resin and polymer components would have remained associated for a sufficiently long time *in vivo* for these investigations to be valid.

In a number of the scintigraphic studies, it was possible to observe qualitative differences in disintegration between these formulations, in terms of the extent of dispersion of the radiolabel seen. The control form was generally seen to disperse readily, whereas the adhesive forms, in particular the Carbopol form, frequently appeared as a small number of clusters of activity. These differences were observed particularly during the first few hours of the investigations. These observations further supported the view that these adhesive agents remained associated with the labelled resins for some considerable time in the GI tract.

The GI transit T values determined for formulation 1 for the two bioadhesives and the non-adhesive control in each subject are summarised in Table 1, and presented in graphical form in Fig. 2. These results showed that the T

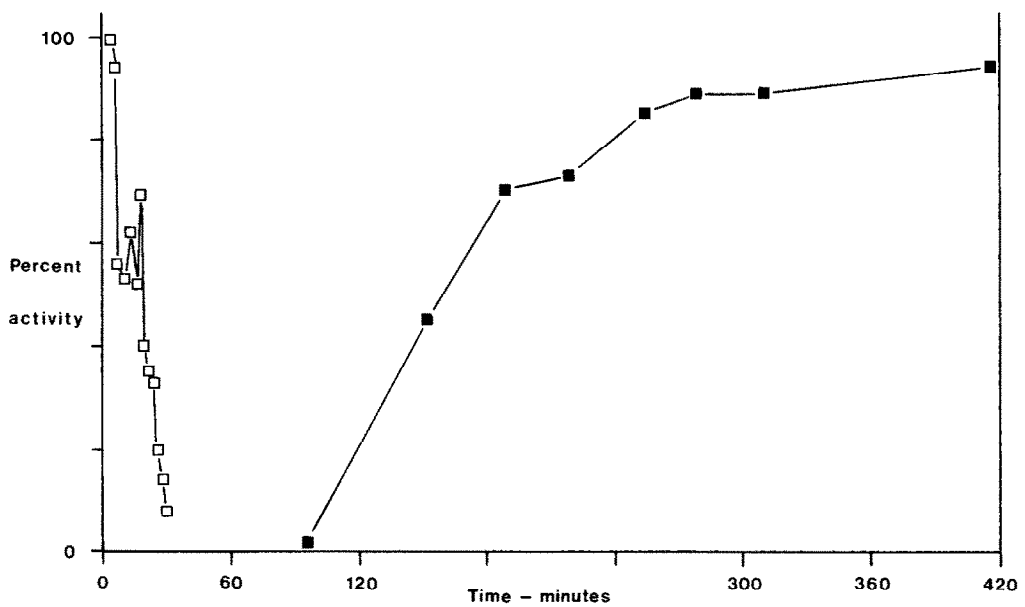

Fig. 1. GI transit of formulation 2 with lactose diluent in one subject: percent activity in stomach (open squares) and colon (closed squares) against time.

TABLE 1

Gastro-intestinal transit $T_{50\%}$ and $T_{90\%}$ values of formulation 1 with two adhesives and one non-adhesive control in 8 human subjects (minutes; $n=8$)

	Bioadhesive or control material	Stomach emptying time (mean ± SE) (range)	Intestinal transit time (mean ± SE) (range)	Arrival time at colon (mean ± SE) (range)
$T_{50\%}$	Polycarbophil	36 ± 11	147 ± 20	(78- 172)
		(3- 82)	(60- 232)	183 ± 24
	Carbopol 934P	82 ± 50	137 ± 11[a]	(105- 265)
		(2- >420)	(105- 175)	170 ± 19[a]
	Lactose	25 ± 11	137 ± 11	(112- 260)
		(1- 75)		162 ± 16
				(80- 230)
$T_{90\%}$	Polycarbophil	54 ± 15	171 ± 34	225 ± 28
		(5- 100)	(95- 285)	(110- 300)
	Carbopol 934P	103 ± 52	150 ± 11	208 ± 31[a]
		(5- 7420)	(115- 180)	(120- 400)
	Lactose	39 ± 12	181 ± 21	220 ± 28
		(5- 100)	(85- 250)	(90- 340)

[a] $n=7$.

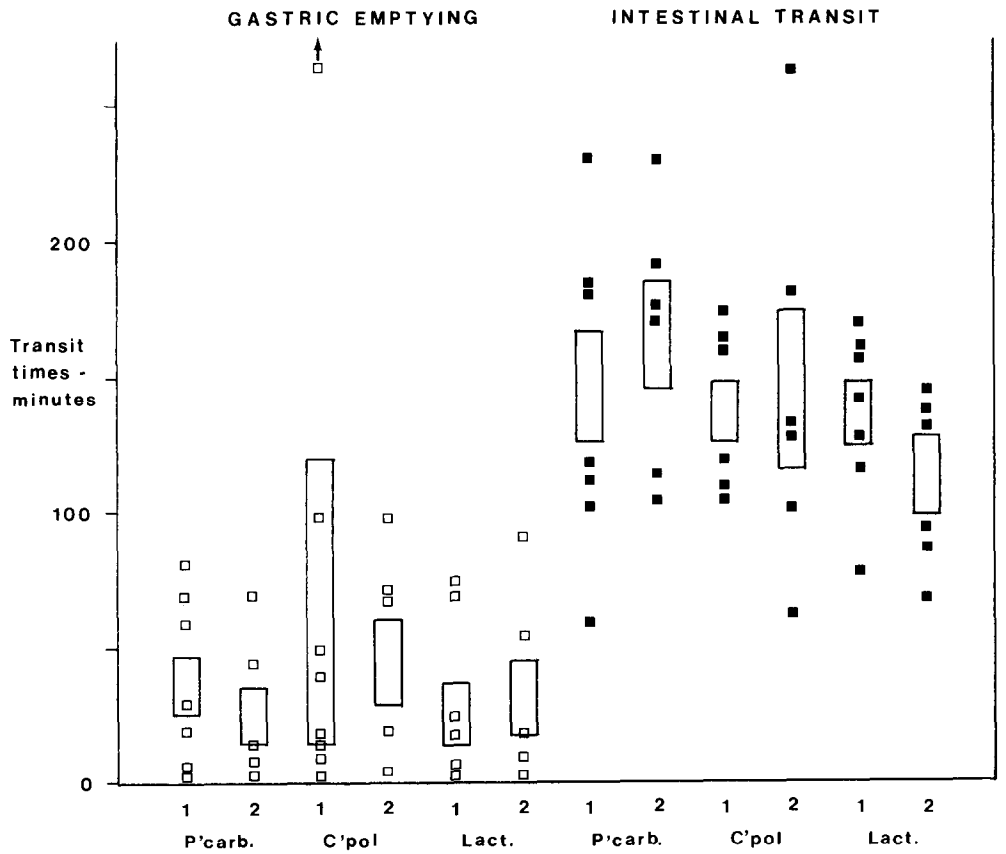

Fig. 2. Gastric emptying and small intestinal transit times ($T_{50\%}$) of formulations 1 and 2 with two adhesives and one non-adhesive diluent (mean ± SE).

TABLE 2

Gastro-intestinal transit $T_{50\%}$ and $T_{90\%}$ values of formulation 2 with two adhesives and one non-adhesive control in 6 human subjects (minutes; $n=6$)

	Bioadhesive or control material	Stomach emptying time (mean ± SE) (range)	Intestinal transit time (mean ± SE) (range)	Arrival time at colon (mean ± SE) (range)
$T_{50\%}$	Polycarbophil	25 ± 11 (3- 70)	165 ± 20[a] (105- 231)	191 ± 25[c] (118- 301)
	Carbopol 934P	45 ± 16 (5- 98)	145 ± 29 (64- 264)	190 ± 21[d] (133- 269)
	Lactose	31 ± 14 (2- 92)	111 ± 13[b] (68- 145)	142 ± 22[e] (77- 237)
$T_{90\%}$	Polycarbophil	33 ± 10 (5- 80)	215 ± 19[a] (125- 280)	248 ± 27[c] (150- 330)
	Carbopol 934P	50 ± 14 (10- 100)	210 ± 28 (120- 325)	200 ± 32[d] (140- 400)
	Lactose	51 ± 14 3- 110	155 ± 31[b] (75- 247)	206 ± 36[e] (80- 300)

a and b differed significantly, $p<0.01$;
c and e differed significantly, $p<0.01$;
d and e differed significantly, $p<0.001$.

transit times for stomach emptying, small intestinal transit and arrival at the colon were similar for all three materials: the GI transit of formulation 1 was essentially unaltered by the agents employed. Paired two-tailed *t*-tests were performed on the results, and none of the differences proved significant at the 5% level. The Carbopol formulation showed a considerably lengthened gastric residence time in one subject. Most of the radiolabel remained in the stomach for 420 minutes after ingestion, at which time the study was terminated. Effects of this order were not observed in any other subjects, nor in the same subject in other investigations. When this one value was excluded from the results, the mean gastric emptying $T_{50\%}$ time (±SE) was 34 ± 13 minutes, which was similar to the means of the polycarbophil and control formulations.

The *T* values determined for formulation 2 for the same three materials are summarised in Table 2, and presented in graphical form in Fig. 2. In contrast to formulation 1, differences were observed between certain of the *T* transit times with formulation 2. In particular, the intestinal transit time for polycarbophil and the colon arrival times for polycarbophil and Carbopol all differed significantly from the corresponding values for the lactose control. These results indicated an increase in oro-caecal transit time of around 30% compared with the control. Inspection of the results suggests that these differences were due to differences in small intestinal transit rather than stomach emptying.

Comparison of the results from formulations 1 and 2 suggests that the differences between materials seen in formulation 2 were due to slower intestinal transit of the polycarbophil and Carbopol forms, coupled with faster intestinal transit of the lactose form: the intestinal transit times for polycarbophil and Carbopol in formulation 2 were only marginally longer than those seen in formulation 1.

It is possible, from the means and standard

TABLE 3

Grouped gastro-intestinal transit results ($T_{50\%}$ and $T_{90\%}$) for two formulations and three excipients in human subjects (minutes: $n=42$)

		Stomach emptying time ($n=42$)	Intestinal transit time ($n=41$)	Arrival time at colon ($n=41$)
$T_{50\%}$	Mean ± SE	42 ± 10	140 ± 7	173 ± 9
	Range	1- >420	60- 264	77- 301
$T_{90\%}$	Mean ± SE	55 ± 9	180 ± 10	227 ± 8
	Range	3- >420	75- 325	80- 400

deviations observed, to estimate the smallest differences which could have been resolved between formulations. By these calculations, these studies would have been able to determine significant differences of 40–60 minutes or more between gastric emptying times, and of around 40 minutes or more between small intestinal transit times.

It appeared, therefore, that the proposed bioadhesives polycarbophil and Carbopol 934P did not greatly affect the transit of either of these formulation types. They certainly did not show the effects which might have been expected from the reports of Robinson and coworkers [17,18], working in the rat. The most likely reason for this disagreement lies in the quantities of polymer administered in the respective studies — 70–150 mg polycarbophil in the rat studies (300–600 mg/kg), compared with 250 mg in man ($\approx$4 mg/kg). Since the poly(acrylic acid)s absorb water and swell greatly above their pK_a [17], the doses administered to rat were probably able to slow GI transit by virtually blocking the tract with their bulk. The results obtained here were in agreement with those of Khosla and Davis [23], working in man, who suggested that the gastric emptying of a formulation similar to formulation 1 was unaffected by polycarbophil.

It is instructive to compare these values with some of the transit times published in the scientific literature for comparable pharmaceutical formulations. Table 3 presents the overall mean GI transit $T_{50\%}$ and $T_{90\%}$ times for both formulations and all three diluents in all subjects. These results showed gastric emptying to be highly variable, both between subjects and also in the same subject on different occasions. Small intestinal transit, on the other hand, showed considerably less variability. These observations were in broad agreement with the findings reported by Davis et al. [1].

CONCLUSIONS

In conclusion, it appeared that the two proposed bioadhesives, polycarbophil and Carbopol 934, considerably slowed the dispersion of these formulations, both *in vitro* and *in vivo*, compared with the control, lactose. The gastric emptying and small intestinal transit of these formulations did not appear to be greatly affected by the type of formulation or by the adhesive or control materials included. These formulations showed similar GI transit times to those reported in the literature for a range of comparable pharmaceutical formulations.

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