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Gastrointestinal transit of a drug-resinate administered as an oral suspension

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Summary

The distribution in the gastrointestinal tract of a radiolabelled drug-resinate formulation, administered in the form of an oral suspension, and the concomitantly administered water wash, was investigated using the technique of dual-isotope gamma scintigraphy. The results demonstrate the influence of the suspension formulation on the gastric emptying and small intestinal transit properties of the drug-resinate complex. Emptying of the suspension formulations from the stomach was independent of the concomitantly administered water wash. In all cases, emptying of the suspension from the stomach was slower than that of the water wash. The distribution of the labelled resinate in the stomach, and subsequent gastric emptying, was influenced by the physical characteristics of the suspension. Although the study was only carried out in a small number of subjects, the small intestinal transit of the non-aqueous suspensions formulated using Migylol was significantly shorter than that of the aqueous suspensions. This may be due to the inclusion of certain pharmaceutical excipients in the formulations. Further work is required to investigate the possibility that these excipients may act as small intestinal cathartics.

Oral administration still constitutes the preferred route for drug delivery, however, many drug substances have an inherently bitter taste. It is well known that patients may not complete a course of treatment if they are prescribed an oral presentation which is particularly unpleasant to taste. Problems associated with the bitter taste of drugs are particularly acute in formulations such as chewable tablets, granules, powders, solutions or suspensions. To some extent, the bitter taste may be masked by the use of sweetening and/or flavouring agents, although this is not entirely satisfactory, and an unpleasant after-taste may still remain in the mouth. In addition, there may be circumstances in which it is undesirable or inappropriate to use a sweetening and/or flavouring agent.

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Various methods have been utilised for masking the bitter taste associated with drug substances, including the use of cationic ion-exchange resins, such as Dowex™ resins (Dow Chemical Co.) or Amberlite™ resins (Rohm & Haas). The drug-resin complex may then be incorporated into an oral dosage form, such as a chewable tablet or a suspension. Aqueous suspensions can be prepared by dispersing the drug-resinate in a suspension of hydroxypropylmethylcellulose (HPMC) or other cellulose derivatives. Non-aqueous suspensions may be obtained by dispersing the drug-resinate in a suitable non-aqueous vehicle, such as fractionated coconut oil, Migylol™ (Dynamit Nobel), with the optional addition of surfactant, such as Span 20, to improve wetting and emulsification of the preparation.

In this work, we report on the use of dual isotope gamma scintigraphy to assess the gastrointestinal (GI) transit behaviour of radiolabelled drug-resinate formulations, administered in the form of oral suspensions, and the concomitantly administered water wash. The drug-resinate complex was prepared from Amberlite IRP-64, a resin with a macroreticular structure and a weak carboxylic acid functionality. However, the resin was poor at binding the trivalent ^{111}In ion, a useful radiotracer in scintigraphic studies. Even under the most advantageous of labelling conditions the binding efficiency was less than 2% for Amberlite IRP-64. Amberlite IRP-69, a similar resin, but with a strong sulphonic acid functional group, has a binding efficiency of 94% with ^{111}In. Therefore, milled Amberlite IRP-69, radiolabelled with ^{111}In, was added to the drug-resinate suspensions as a surrogate marker for drug-resinate complex. Previous in vitro studies indicated that the particle size of the marker and drug-resinate complex were similar and the marker easily and evenly distributed throughout the suspension preparation. The radiolabelled resin (5 mg per unit dose) was mixed with each suspension on the morning of each of the study days.

Each 5 ml of the non-aqueous suspension contained 500 mg of drug-resinate complex and several pharmaceutical excipients, in particular xylitol as a bulk sweetener. Span 20 was added to one of the two non-aqueous suspensions. Each 10 ml of the aqueous suspension contained 500 mg of drug-resinate complex in a 5% HPMC solution.

This was an open randomized three period cross-over study carried out in six male subjects (age range 19–23 years). Each subject provided written informed consent to participate in the study. The study was approved by the Quorn Research Review Committee and approval for the administration of radiolabelled formulations was obtained from the Department of Health, London. The following doses were administered after an overnight fast:

(i) Aqueous suspension (10 ml) containing 500 mg of drug-resinate complex;
(ii) Migylol™ suspension (5 ml) containing 500 mg of drug-resinate complex;
(iii) Migylol™/Span 20 suspension (5 ml) containing 500 mg of drug-resinate complex.

The aqueous suspension and the non-aqueous suspensions were administered orally with a water wash which consisted of 190 ml or 195 ml of deionised water, depending on the suspension dose volume. The water wash was radiolabelled with 4 MBq ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), a non-absorbable marker material, to provide a measure of liquid gastric emptying and intestinal transit. In addition, the dispersion of the water wash throughout the GI tract was used to identify the anatomy of the stomach and intestines.

Anterior and posterior scintigraphic images, each of 60 s duration, were taken every 5 min for the first 30 min of the study. Subsequently, images were acquired every 15 min until lunch and then every 30 min until the end of the study period. The gamma camera had a 40 cm field of view and was fitted with a medium energy (300 keV) parallel-hole collimator. Images were recorded on a computer and stored on magnetic tape for analysis at a later stage (Coupe et al., 1991a). No breakfast was permitted but thereafter the subjects received a standard diet, which was identical for each study period. Each volunteer drank 200 ml of water 2 h post-dose. A light lunch was provided 4 h post-dose and dinner at

TABLE 1

Gastrointestinal transit of the drug-resinate administered as an aqueous suspension

Vol. no.	Gastric emptying $T_{50\%}$ (min)		Gastric emptying $T_{90\%}$ (min)		Intestinal transit $T_{50\%}$ (min)	
	Resinate	Water wash	Resinate	Water wash	Resinate	Water wash
1	28	10	47	28	220	201
2	27	7	46	28	116	136
3	42	12	82	39	190	179
4	18	11	47	21	248	255
5	55	10	105	79	192	230
6	29	12	38	38	108	121
Mean	33	10	61	39	179	187
SD	13	2	27	21	56	52
Median	29	11	47	33	191	190

10 h post-dose. Fluids were allowed ad libitum after lunch

The suspension formulations did not disperse entirely in the stomach contents immediately on dosing; with the exception of the aqueous suspension in subject 2. Overall, the aqueous formulation tended to move from the fundus to the antrum becoming more dispersed during the migration process. The Migylol™ non-aqueous suspensions without Span 20, however, tended to mix poorly with the stomach contents and split into a number of distinct portions, without actually becoming fully dispersed in the gastric milieu. This is consistent with the behaviour of a poorly wetted material and, assuming that (ion) exchange of drug requires direct contact with acid, then the lack of dispersion for this formulation may provide a significant barrier to drug release and could subsequently delay or reduce absorption.

The Migylol™/Span 20 non-aqueous suspensions had better mixing properties in the gastric media, than the formulation without Span 20, presumably due to the improved wetting/emulsification of the formulation imparted by the inclusion of the surfactant. However, in the majority of subjects, a large proportion of the formulation resided in the fundus of the stomach, typically for longer than observed for the aqueous system. This prolonged residence time in the upper portion of the stomach was surprising. It appears unlikely that the suspensions are floating on the stomach contents, since their specific gravity is typically 1.05 and the relative density of gastric juice only 1.00–1.01 (Leach, 1961). Previous studies (Washington et al., 1989) have shown

TABLE 2

Gastrointestinal transit of the drug-resinate administered as a non-aqueous suspension

Vol. no	Gastric emptying T_{50} (min)		Gastric emptying $T_{90\%}$ (min)		Intestinal transit $T_{50\%}$ (min)	
	Resinate	Water wash	Resinate	Water wash	Resinate	Water wash
1	115	16	148	115	146	245
2	14	10	60	25	110	111
3	61	39	139	121	151	173
4	23	15	32	30	93	105
5	94	18	138	103	138	214
6	32	11	78	42	61	107
Mean	57	18	99	73	117	159
SD	41	11	49	45	35	61
Median	47	16	108	73	124	142

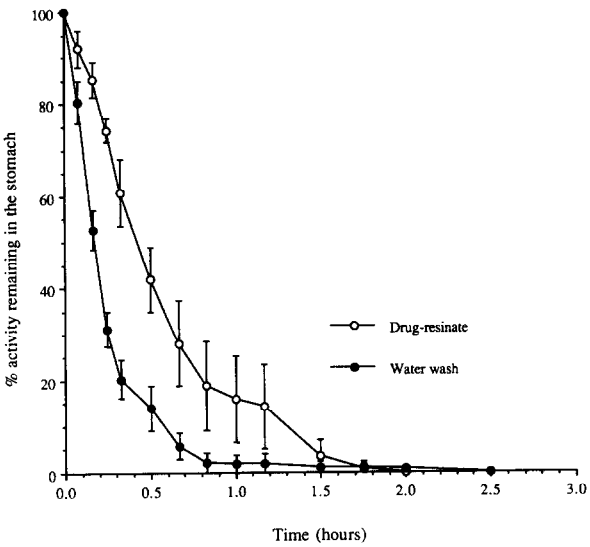

Fig. 1. Gastric emptying of the drug-resinate administered as an aqueous suspension ($n = 6$, SE).

that small particles delivered to the stomach by rapidly dissolving tablets (Expidet™) exhibit delayed gastric emptying compared to the same particles delivered either as a chewable tablet or antacid preparation. However, the in vivo behaviour of small particles delivered in a viscous medium, such as a suspension, has not been evaluated and it is possible that the resinate may become initially trapped in the folds of the stomach wall and then passively redistribute due to gravity. Direct association between the suspension liquid phase or the resinate and the mucus layer may also occur (Washington et al., 1989).

The gastric emptying data for both the drug-resinate complex and the water wash have been expressed as the time for 50% ($T_{50\%}$) and the time for 90% ($T_{90\%}$) of activity to leave the stomach. Intestinal transit of the preparations has been calculated by subtracting the $T_{50\%}$ for gastric emptying from the corresponding value for colon arrival. The GI transit data for the three different formulations are presented in Tables 1–3 and the mean gastric emptying profiles are provided in Figs 1–3.

Gastric emptying of the drug-resinate suspensions can be considered to be independent of the concomitantly administered water wash. In all cases, emptying of the suspension from the stomach was slower than that of the wash. Small liquid volumes administered to a fasted stomach will mix with gastric contents and empty rapidly. Emptying of nonnutrient liquids is reported to follow a first-order process (Bateman and Whittingham, 1982) and is dependent upon the initial administered volume (Hunt and MacDonald, 1954). Liquid emptying is therefore rapid and the gastric emptying results reported for the water wash in this study (mean $T_{50\%}$ values less than 20 min for all formulations) are in good accord with the literature data. There appears to be slight differences between the liquid emptying time seen with the aqueous and non-aqueous suspensions (mean $T_{50\%}$ 10 min compared to 17 and 18 min).

TABLE 3

Gastrointestinal transit of the drug-resinate administered as a non-aqueous suspension (with Span 20)

Vol. no.	Gastric emptying $T_{50\%}$ (min)		Gastric emptying $T_{90\%}$ (min)		Intestinal transit $T_{50\%}$ (min)	
	Resinate	Water wash	Resinate	Water wash	Resinate	Water wash
1	69	7	134	31	146	194
2	88	23	142	100	75	113
3	80	7	145	35	86	148
4	45	31	93	65	108	122
5	59	9	124	47	96	148
6	46	24	114	84	78	96
Mean	65	17	125	60	98	137
SD	18	10	20	23	26	35
Median	64	16	129	56	91	135

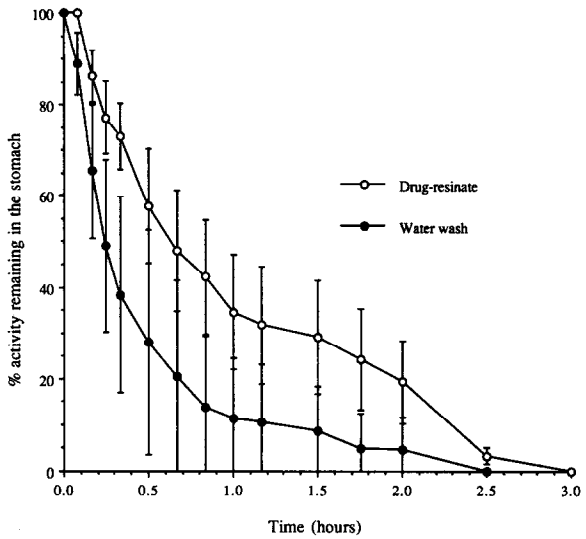

Fig. 2. Gastric emptying of the drug-resinate administered as a non-aqueous suspension ($n = 6$, SE).

It would appear that the suspension formulations are not behaving as true 'liquids' with respect to gastric emptying and therefore they may, in part, be dependent on the migrating myoelectric complex (MMC) for gastric emptying (Kelly, 1981). Administration of the formulation during phase 3 of the contractions would result in a very rapid emptying profile whilst dosing during phase 1 of the MMC, when there are no contractions, would lead to considerably slower emptying (Oberle et al., 1990). However, it must be remembered that gastric emptying, under the control of a 'phase 3 process', is not always efficient (Coupe et al., 1991b). For example, material may remain in the less muscular body of the stomach and may not be propelled into the antrum where emptying can take place.

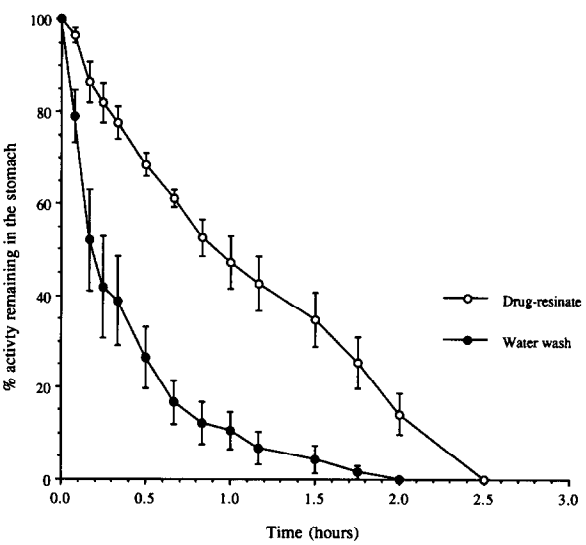

Fig. 3. Gastric emptying of the drug-resinate administered as a non-aqueous suspension (with Span 20) ($n = 6$, SE).

Changing the nature of the suspension from aqueous to non-aqueous did appear to slow the emptying properties of the resinate, which may be a function of the different spreading properties of the formulation in the stomach. It is possible that the fatty component of the oil based suspensions could be altering the motility pattern of the stomach. The incorporation of myristic acid (or its salts) into a tablet formulation has been shown to delay the renal excretion of a coadministered drug, which suggests a slowing of gastric emptying induced by the fatty acid (Groning and Heun, 1984, 1989). Subjects who received the Migylol™/ Span 20 suspension typically showed a gradual emptying over time, similar to that observed for the solid phase of food.

The average small intestinal transit time was approx. 2–3 h. Scintigraphic evaluation of a large number of diverse formulations has shown that transit of pharmaceutical dosage forms through the small intestine is independent of feeding conditions and physical properties of the system and that the average time is 3 h with a standard deviation of 1 h (Davis et al., 1986). Small differences were observed in the transit times for the water wash following administration with the suspension formulations. However, changing the nature of the suspension from aqueous to non-aqueous had an effect on the rate of transit of the resinate in the small bowel. Addition of Span 20 to the formulation did not significantly alter the small intestinal transit properties of the non-aqueous system. It is postulated that one or more of the excipients used in the non-aqueous suspensions may act as small intestinal cathartics. However, the caveat of small sample sizes should be remembered; recent studies have shown significant inter- and intra-subject variability in both

gastric emptying and small intestinal transit (Coupe et al., 1991a).

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