The effects of pharmaceutical excipients on small intestinal transit

D. A. ADKIN¹, S. S. DAVIS^{1,2}, R. A. SPARROW³, P. D. HUCKLE⁴, A. J. PHILLIPS⁴ & I. R. WILDING²

¹Department of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham, NG7 2RD,

²Pharmaceutical Profiles Limited, 2 Faraday Building, Highfields Science Park, Nottingham, NG7 2QP, ³Department of Human Morphology, Queens Medical Centre, Clifton Boulevard, Nottingham, NG7 2UH and ⁴Pharmaceutical Development Department, Pharmacy Division, Glaxo Group Research, Park Road, Ware, SG12 0DP

- 1 The effect of three iso-osmotic pharmaceutical excipient solutions on gastrointestinal transit were investigated in eight healthy male volunteers. Each subject received 200 ml radiolabelled purified water, or a 200 ml solution of sodium acid pyrophosphate ((SAPP) 1.1 g/200 ml), mannitol (2.264 g/200 ml) or sucrose (4.08 g/200 ml) in a four way cross over design. On each of the study days the volunteers also received five 6 mm diameter non-disintegrating tablets. Dual isotope gamma scintigraphy was used to assess the transit behaviour of the tablets and solutions.
- 2 There were no significant differences between the gastric emptying times of the four solution formulations. Rapid gastric emptying was observed in all cases (mean t 50% varied from 11–14 min).
- 3 Small intestinal transit (SIT) times for the SAPP and mannitol solutions were reduced by 39 and 34%, respectively, when compared with the control solution (purified water = 240 min; SAPP = 147 min; mannitol = 158 min). The 95% confidence limits for the mean differences in SIT time between the control and SAPP solutions was 39–94–149 min, and 40–82–124 min between the mannitol and the control. Intestinal transit for the sucrose solution was similar to that for the control solution (sucrose = 229 min).
- 4 There were no significant differences in the transit times of the non-disintegrating tablet preparations, when co-administered with each solution.
- 5 The intestinal transit data for the SAPP and mannitol solutions demonstrate that excipients may alter gastrointestinal transit at low concentrations relevant to pharmaceutical formulation, and may therefore be a factor in reducing the absorption of certain drugs.

Keywords sodium acid pyrophosphate mannitol sucrose small intestinal transit gamma scintigraphy

Introduction

Drug absorption from the gastrointestinal (GI) tract is a complex process subject to many variables [1]. The small intestine is still generally regarded as the main site of drug absorption in man [2]. The stomach and the colon contribute much less to the extent of absorption of orally administered compounds. Small intestinal transit (SIT) time has been demonstrated

to be consistently around 3–4 h [3–7]. As a consequence, if a drug is absorbed exclusively from the small intestine, then there is only a relatively short period in which absorption can occur [8].

The physicochemical characteristics of the drug and the pharmaceutical excipients incorporated in the formulation are also key determinants of drug absorp-

tion. The principal aims of formulation are to achieve optimum bioavailability, extended duration of action and reduced drug toxicity [9]. Few studies have investigated the effect that pharmaceutical excipients may have on the GI transit of the dosage form [10, 11]. As a consequence it has been largely assumed that excipients, at concentrations relevant to pharmaceutical formulation, do not alter intestinal transit. However, during development of a ranitidine effervescent oral solution dosage form, a marked decrease was observed in the extent of drug absorption relative to the conventional oral tablet [12]. The extent of ranitidine absorption was approximately halved with formulations that contained 1132 mg of sodium acid pyrophosphate (SAPP) compared with those formulated without SAPP. Two separate gamma scintigraphy studies conducted in healthy volunteers confirmed that 1132 mg of SAPP was capable of reducing SIT time by 43%, and was, therefore, influencing drug bioavailability by reducing contact time of the drug solution with the absorbing membrane in the small bowel. The objective of the present study was to examine in further detail the effect of excipients on intestinal transit.

Sorbitol, a polyalcohol sugar is frequently used in the formulation of oral medications. Consumption of excessive amounts, 20 to 50 g, has been reported to cause diarrhoea [13]. Smaller quantities have been shown to cause GI distress [14]. Xylitol, another pharmaceutical excipient has been shown to reduce SIT time [11, 15]. Chewable and effervescent oral formulations tend to utilise sugar alcohols like sorbitol, xylitol and mannitol to mask the unpleasant taste of some drugs. The quantities utilised in pharmaceutical formulation vary, but it is not unusual to find concentrations of 2 g per unit dosage form. Therefore, if these quantities of excipient are to be used in formulation, it is essential to understand the effect that they may have on the *in vivo* transit of the dosage form.

In this study, we have used the technique of dual isotope gamma scintigraphy to follow the GI transit of purified water BP and three iso-osmotic pharmaceutical excipient solutions of SAPP, mannitol and sucrose. The excipient solutions were co-administered with non-disintegrating single unit dosage forms, with the aim of evaluating the effect of the excipients on both solid and liquid transit.

Methods

Subjects

The study was carried out in eight, healthy males (22–28 years) who were non-smokers and were not on any medication. Each volunteer gave written informed consent to participate in the study. The volunteers were not allowed to consume alcohol during the study period, or in the preceding 24 h. The experimental protocol was approved by the ethics committee of the University of Nottingham and the

study was conducted in accordance with the Declaration of Helsinki guidelines for ethics in research. Approval to administer the radiopharmaceuticals was obtained from the Department of Health.

Radiolabelling of dosage forms

Non-disintegrating tablets (6 mm diameter, 140 mg weight) were prepared from ethylcellulose containing 2% Amberlite resin IRP-169 (BDH, Poole, Dorset). The resin was radiolabelled with ^{111}In and then sieved prior to blending with ethylcellulose (BDH, Poole, Dorset). The powder mixture was compressed using a Manesty F3 single punch tablet machine to produce round, shallow, concave tablets with an activity of 0.2 MBq of ^{111}In per tablet at the time of administration. The tablets were coated to prevent leaching of the radiolabel and *in vivo* disintegration [16].

Previous studies on effervescent formulations have demonstrated that 1132 mg of SAPP was capable of altering intestinal transit [12] and, therefore, this was used as a reference amount in this investigation. Iso-osmotic solutions of the three excipients were prepared to reduce the factors that could influence transit behaviour. The osmolality of the three excipient solutions was measured using an Osmomat 030 cryoscopic osmometer, and found to be $0.063 \text{ Osmol kg}^{-1}$. The iso-osmotic test solutions of SAPP, mannitol and sucrose were freshly prepared with purified water on each study day. Each 200 ml aliquot of excipient solution was radiolabelled with 4 MBq of $^{99}\text{Tc}^{\text{m}}$ diethylenetriaminepentaacetic acid (DTPA) (< 0.2 ml).

Study protocol

Each subject was studied on four separate occasions; at least 48 h apart. On each of the study days, the subjects received the preparations after an overnight fast. Each volunteer received five radiolabelled tablets and a 200 ml radiolabelled excipient solution following the dosing regime outlined below:

Study day 1: Purified water BP (200 ml) Control formulation

Study day 2: SAPP (1.100 g/200 ml) solution

Study day 3: Mannitol (2.264 g/200 ml) solution

Study day 4: Sucrose (4.080 g/200 ml) solution

No additional food or fluid was allowed until 4 h after dosing, when the volunteers received a standard lunch (3800 kJ).

Small ^{111}In -labelled anatomical reference markers were taped to the skin anteriorly and posteriorly over the right lobe of the liver. Immediately after dosing, anterior and posterior images, each of 60 s duration, were recorded approximately every 10 min until all the tablets and solution had reached the colon. The gamma camera (General Electrical Maxi-Camera) had a 40 cm field of view and was fitted with a medium energy parallel hole collimator. The images were recorded using a Bartec computer system and stored on magnetic tape for subsequent analysis.

Data analysis

Each image was aligned with the anatomical reference markers. Dispersion of the solution enabled delineation of the stomach and colonic region, relative to the anatomical marker, and the subsequent position of the tablets in the GI tract could be identified. Gastric emptying (GE) and colon arrival (CA) of the tablet preparations was an all or nothing process. The time of movement of the tablet preparation from one anatomical region to the next was taken as the midtime between recording the two images about the transition.

GE and CA of the solution formulations was determined by identification of the stomach and colon anatomy from the series of acquired images. Regions of interest were constructed around the stomach and/or colon and the activity quantified. A further region of interest was drawn on each image, away from the main activity, to allow for the correction of background activity. When employing dual isotope imaging with ^{111}In and $^{99}\text{Tc}^{\text{m}}$ a correction is required for the 'scatter-down' of the activity of the higher energy (^{111}In) into the energy window of $^{99}\text{Tc}^{\text{m}}$. The data were also corrected for radioactive decay. The attenuation of the radiation by overlying tissues can give rise to incorrect estimates of the amounts of radioactivity in the regions of interest, however, this was overcome by calculating the geometric mean of the anterior and posterior counts, which gave a result that was relatively independent of the depth of the source [17]. GE time for the solutions was taken as the time for 50% to empty from the stomach, and CA was taken as the time for 50% to arrive in the caecum. SIT times were taken as the difference in time between 50% of the solution arriving in the colon and 50% of the solution leaving the stomach.

Statistical analysis was performed on the GE, CA and SIT times for both the tablets and the excipient solutions. A paired Student's *t*-test and 95% confidence limits were used to compare the excipient transit data with that of the control preparation.

Results

Gastrointestinal transit of the solutions

On ingestion, the solution formulations dispersed rapidly throughout the stomach. GE began immediately and followed an exponential model, as described previously [18]. The GE *t*50% times of the purified water BP, SAPP, mannitol and sucrose, are shown in Table 1. The mean *t*50% times for the solutions ranged from 11 to 14 min. The paired Student's *t*-test showed there was no significant difference between the GE *t*50% times of the 4 solutions; (Control vs SAPP, *P* = 0.334; Control vs mannitol, *P* = 0.425; Control vs sucrose, *P* = 0.872).

The SIT data for the solutions are shown in Table 2. The *t*50% times for SIT of the control formulation were in the range of 134 to 449 min, with a mean value of 240 min and a median of 237 min. The mean *t*50% times for the SIT of the SAPP and mannitol solutions were 147 and 158 min, respectively, which were significantly different from the control preparation (Control vs SAPP, *P* = 0.012; Control vs mannitol, *P* = 0.006). SIT time for the SAPP and mannitol solutions was reduced by 39 and 34%, respectively, when compared with the purified water. The sucrose solution did not appear to alter the SIT rate; the mean transit time of 229 min was comparable with that of the control formulation. The SIT data for the four solutions in each subject are shown schematically in Figure 1.

The CA data for the solutions (Table 3), followed a similar trend to the SIT results. The SAPP and mannitol solutions had mean *t*50% CA times of 161 and 172 min, respectively, which were significantly different from that of the control formulation, which had a mean *t*50% CA time of 251 min, (Control vs SAPP, *P* = 0.015; Control vs mannitol, *P* = 0.008).

Gastrointestinal transit of the tablet preparations

All the tablets passed from mouth to anus intact in all the volunteers on each of the study days. Regrouping

Table 1 Gastric emptying times (min) for 50% of the radiolabelled solutions following administration to eight fasted male volunteers

Volunteer	Purified water BP	SAPP 1.10 g/200 ml	Mannitol 2.264 g/200 ml	Sucrose 4.08 g/200 ml
1	15	20	37	20
2	8	7	9	8
3	7	11	14	14
4	16	22	16	16
5	14	11	11	10
6	7	7	8	7
7	14	7	7	8
8	7	26	7	7
Mean	11	14	14	11
s.d.	4	8	10	5
Median	11	11	10	9

Figure 1 Small intestinal transit times for 50% of the radiolabelled solutions (○ water, ● SAPP, ■ mannitol and □ sucrose) after administration to fasted volunteers.

and stagnation of the tablets at the ileocaecal junction occurred in all volunteers. Table 4 shows the GE, CA and SIT $t_{50\%}$ times for the tablet preparations when co-administered with each excipient solution. There were no statistical differences in any of the tablet transit data.

Discussion

In the fasted state, the emptying behaviour of the stomach is controlled by a phenomena known as the migrating myoelectric complex (MMC) [12–21]. The MMC is usually divided into four phases of activity [5], which recur approximately every 2 h. However, these immediately cease upon the ingestion of food. Phase III of the MMC is known as the ‘housekeeper wave’, and acts to empty the stomach of swallowed saliva, cellular debris, and indigestible solids. The MMC continues from the stomach into the small

Table 2 Small intestinal transit times (min) for the radiolabelled solutions following administration to eight fasted male volunteers

Volunteer	Purified water BP	SAPP 1.10 g/200 ml	Mannitol 2.264 g/200 ml	Sucrose 4.08 g/200 ml
1	242	134	197	248
2	245	151	156	245
3	258	164	198	253
4	449	194	229	249
5	231	125	164	252
6	165	78	82	193
7	134	111	113	157
8	197	215	127	238
Mean	240	147	158	229
s.d.	95	45	49	35
Median	237	143	160	247

95% Confidence limits for mean differences in transit time.

Control vs SAPP 39–94–149 min.

Control vs mannitol 40–82–124 min.

Table 3 Colon arrival times (min) for 50% of the radiolabelled solutions following administration to eight fasted male volunteers

Volunteer	Purified water BP	SAPP 1.10 g/200 ml	Mannitol 2.264 g/200 ml	Sucrose 4.08 g/200 ml
1	257	154	233	268
2	253	157	165	253
3	265	175	212	267
4	464	217	245	265
5	245	136	175	262
6	172	85	90	200
7	148	118	120	165
8	205	241	134	244
Mean	251	161	172	240
s.d.	96	51	56	38
Median	249	156	170	258

95% Confidence limits for mean differences in transit time.

Control vs SAPP 36–91–146 min.

Control vs mannitol 37–79–111 min.

Table 4 Small intestinal transit, gastric emptying and colon arrival times (min) for 50% of the tablet preparations following administration to eight fasted male volunteers

Volunteer	Purified water BP	SAPP 1.10 g/200 ml	Mannitol 2.264 g/200 ml	Sucrose 4.08 g/200 ml
<i>Gastric emptying</i>				
Mean	52	53	31	44
s.d.	46	44	29	31
Median	26	42	25	32
<i>Small intestinal transit</i>				
Mean	198	158	166	200
s.d.	76	59	48	35
Median	199	147	176	202
<i>Colon arrival</i>				
Mean	250	211	197	244
s.d.	96	62	61	33
Median	249	228	202	256

intestine, and as one complex reaches the ileum, another starts at the duodenum [22].

In this investigation, gastric emptying of the solution and the tablet formulations occurred at different rates. The solutions emptied rapidly, whilst the tablets remained in the stomach for a considerable time. The gastroduodenal pressure produced by the slow, sustained contraction of the proximal stomach controlled the emptying of the solutions [23]. The tablets were probably treated as indigestible solids, and since the volunteers were fasted at the time of administration, subsequent gastric emptying of the tablets was probably due to phase III of the MMC [24, 25]. If the tablets were administered just before a 'housekeeper wave', then they would be rapidly emptied from the stomach. However, if they were administered just after phase III activity then it is probable that the tablets would not be emptied until the next 'housekeeper wave' occurred some 2 h later. Subjects 4, 5 and 7 on the control study day appear to have been dosed just after a 'housekeeper wave', since extended gastric emptying times were noted when compared with the other subjects, who emptied in the range of 15 to 26 min. The gastric emptying $t_{50\%}$ times of the tablet preparations are in line with previous reports on the emptying of single unit dosage forms from the fasted stomach [26, 27].

The mean small intestinal transit time of purified water BP was 240 min, which is good agreement with previous findings [7]. However, both SAPP and mannitol acted as small intestinal cathartics, in amounts that represent those normally used in the formulation of chewable tablets.

The pharmaceutical excipient, sorbitol has been shown to cause diarrhoea [10]. This may be due to the osmotic potential of the unabsorbed sugar causing large volumes of water to be retained by the small bowel [28] and/or the impaired colonic reabsorption of water resulting from the increased osmolality of the acid metabolites of bacterial fermentation [29]. Although the SAPP and mannitol solutions did not cause diarrhoea in any of the volunteers, perhaps the

mechanism by which they caused small intestinal transit acceleration is similar to that which causes sorbitol induced diarrhoea. Mannitol and other sugar alcohols are incompletely digested in the small intestine [30–32]. The residual amounts reaching the colon are digested by colonic bacteria or excreted in the stools. Previous studies have shown mannitol to have a laxative effect, with a 'threshold dose' of 10 to 20 g [33]. The mannitol could, therefore, maintain an increased volume of fluid in the lumen of the small intestine by osmosis [33], with the principle effect of accelerating the transfer of gut contents through the small bowel. SAPP could be acting as a saline cathartic [34]. These act by increasing the osmotic load of the GI tract, resulting in increased bulk, which may stimulate peristalsis [35]. The normal dose range for a phosphate salt, saline cathartic is 4 to 8 g, the SAPP solution in this study caused an acceleration of small intestinal transit at a dose below this range. The precise mechanism by which mannitol and SAPP as excipients exert their cathartic effect requires further investigation.

Sucrose had no effect on small intestinal transit rate. The epithelial cells lining the small intestine produce enzymes which are capable of cleaving sucrose into its constituent monosaccharides, glucose and fructose [36]. These enzymes are located in the brush border, and disaccharides like sucrose are digested as they come into contact with the epithelial lining. The monosaccharides, fructose and glucose are then rapidly absorbed into the portal blood [37]. Therefore, the sucrose solution is metabolised and absorbed in the proximal small intestine, and this probably explains the lack of cathartic effect with this excipient.

The lack of significant differences in the transit data for the tablets on all 4 study days was not anticipated, since it was expected that there would be some correlation between the data for solid and liquid transit. Previous studies have shown that solids and liquids move through the small intestine at the same rate [7, 38]. However, our results may be explained

by the delayed gastric emptying of the tablets compared with the solutions. In many cases, the excipient solutions moved through the small intestine ahead of the tablets, and as a consequence tablet transit was not influenced by the excipient incorporated in the solution. The effect of both mannitol and SAPP on intestinal transit was transitory, which supports the suggestion that increased volume of fluid retained in the lumen is responsible for the cathartic action. Subsequent studies (unpublished) have been undertaken to investigate the effect of mannitol administered as either solution or chewable tablet on cimetidine absorption. The results of these studies show that the presence of mannitol does alter the transit of suspended drug particles because reduced drug absorption, as well as increased small bowel transit, were observed with the mannitol formulations compared with the control preparations.

The stratification of the study design does not entirely preclude possible order effects in the intestinal transit data. However, it would be difficult to explain the magnitude of the differences observed for both SAPP and mannitol by simple carry-over effects. In addition, subsequent randomised studies have shown that the same concentration of mannitol (2.264 g/200 ml) has consistently reduced SIT transit by 34% [39].

As noted by others [40, 41] regrouping and stasis of the tablets occurred at the ileocaecal junction in all volunteers. The human terminal ileum acts as a reservoir for solids, since transfer of residue to the colon occurs in boluses [42]. The pattern of ileocolonic transit is slower and more erratic before a meal than postprandially [43]. The effect of eating on terminal ileal motility is generally limited to the initial 30 min of the postprandial period [43, 44]. The bolus transfers are especially frequent within 30 min of ingestion of a meal. The colon arrival times for the tablets on the 4 study days were similar, which could be explained by the fact that lunch was always administered 4 h after dosing and, therefore, each volunteer received the stimulus for increased flow across the ileocaecal junction at approximately the same time. Subject 4 had an unusually long small intestinal transit time on the control study day. This was probably due to extended stasis at the ileocaecal junction of the solution and tablets, caused by the preparations reaching the terminal ileum after lunch.

This study has shown that SAPP and mannitol influence intestinal transit at concentrations relevant to pharmaceutical formulation. Both excipients would reduce the residence time of drugs, incorporated in formulations in the small intestine, and could thereby influence their absorption.

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