The Effect of Polyethylene Glycol 400 on Gastrointestinal Transit: Implications for the Formulation of Poorly-Water Soluble Drugs

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Purpose. To assess the effect of polyethylene glycol 400 (PEG 400), a pharmaceutical excipient frequently employed to enhance the solubility and bioavailability of poorly water-soluble drugs, on the gastrointestinal transit of liquid and pellet preparations in human subjects using gamma scintigraphy.

Methods. Ten, healthy male volunteers each received, on separate occasions, a liquid preparation consisting of 150 ml orange juice (control) or 150 ml orange juice containing 10 g PEG 400 (test). Non-disintegrating pellets of size 1.4–1.7 mm, encapsulated within a hard gelatin capsule, were simultaneously administered on both occasions to act as a marker for solid dosage form transit. The liquid and pellet preparations were radiolabelled with ^{111}In and ^{99m}Tc respectively thus enabling their positions within the gastrointestinal tract to be followed using a gamma camera.

Results. Rapid liquid emptying from the stomach was observed, with no significant difference noted in the gastric residence times of the two preparations. Caecum arrival times for the liquid preparations were significantly different by virtue of their differential rates of transit through the small intestine. The mean small intestinal liquid transit time for the control preparation was 236 min whereas the corresponding value for the PEG 400-containing test preparation was 153 min. This 35% reduction in transit time was attributed to the presence of PEG 400. Pellet transit was largely unaffected by the presence of PEG 400.

Conclusions. These findings clearly demonstrate that PEG 400 has a marked accelerating effect on small intestinal liquid transit, which in turn has implications for the formulation of poorly water-soluble drugs with PEG 400.

KEY WORDS: polyethylene glycol 400; poorly water-soluble drugs; co-solvent; gastrointestinal transit; absorption; gamma scintigraphy.

INTRODUCTION

The absorption of drugs from the gastrointestinal tract is a complex process subject to many factors. One well-established factor is that of drug solubility. Poorly water-soluble drugs often exhibit low oral bioavailabilities as a consequence of limited dissolution within the gastrointestinal tract. A variety of physico-chemical and formulation strategies are available to enhance the solubility of such drugs (1). One of the more straight-forward and commonly used approaches involves the water-miscible liquid polymer polyethylene glycol 400 (PEG 400) as a solvent or co-solvent. Poorly water-soluble drugs are thus routinely solubilised using PEG 400 and presented in the form of soft gelatin capsules or simple liquid formulations to enhance their bioavailability. In addition, during early stage pharmacokinetic evaluation in animals or humans, the absorption potential of new drug molecules is often assessed in the presence of copious quantities of solubility-enhancing vehicles such as PEG 400. Although PEG 400 has been widely used in these respects, in some cases the results have been less than successful. For example, although the solubility of the antifungal drug griseofulvin was considerably improved by the presence of 10 g of PEG 400 in a liquid formulation, the bioavailability of the drug, in rabbits, was strikingly lower from this liquid formulation than from a conventional powder-filled hard gelatin capsule formulation (2). The authors postulated that this anomaly was due to possible differences in the gastrointestinal transit of the two formulations rather than precipitation of the drug from the liquid formulation. The present study was therefore undertaken to assess the effect of 10 g of PEG 400 on the gastrointestinal transit of liquid and pellet preparations in human subjects using the non-invasive technique of gamma scintigraphy.

MATERIALS AND METHODS

Preparation and Radiolabelling of Dosage Forms

A multi-unit preparation consisting of pellets was used as a model for solid dosage form transit. The pellets were prepared from a formulation consisting of microcrystalline cellulose (Avicel PH101, FMC Corp., Philadelphia, USA), barium sulphate (Sachtleben Chemie GmbH, Duisberg-Homberg, Germany) and 5% of the ion-exchange resin, amberlite CG 400 (Sigma-Aldrich Company, Poole, UK) by the process of extrusion-spheronisation. The resultant pellets were screened according to size and only pellets within the size fraction 1.4–1.7 mm were used. The pellets were coated using a fluidised bed coater (model Strea-1, Aeromatic AG, Bubendorf, Switzerland) with a mixture of ethylcellulose (Surelease EA-7100, Colorcon, Dartford, UK) (80%) and methylcellulose (Methocel A Colorcon, Dartford, UK) (20%) to a total weight gain of 4%. The pellets were subsequently radiolabelled with technetium-99m (^{99m}Tc) by soaking in a solution of sodium pertechnetate. Pellet integrity, in terms of non-disintegration and radiolabel stability, was assessed *in vitro* using dissolution tests under simulated gastrointestinal conditions (3). The pellets released less than 5% of the radiolabel over a period of 24 h and remained intact throughout the course of the dissolution experiment, thereby confirming their suitability for *in vivo* administration. The labelled pellets were filled into size 0 hard gelatin capsules (Capsugel, Colmar, France) to a nominal fill weight of 300 mg. The encapsulated pellets had an activity of 7.4 MBq at the time of administration.

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The liquid preparation consisted of 150 ml orange juice (Tesco Stores Ltd., Cheshunt, UK). Each aliquot of orange juice contained either 0 or 10 g of PEG 400 (Sigma-Aldrich Company, Poole, UK). Orange juice rather than water was used as a model for liquid transit to mask the bitter taste of PEG 400. Each liquid preparation was radiolabelled with indium-111 (^{111}In) to an activity of 2.5 MBq using ^{111}In-diethylenetriaminepentaacetic acid (^{111}In-DTPA) solution. The osmolality of the two liquid preparations was measured using an osmometer (model 200, Camlab, Cambridge, UK). The osmolality of the orange juice was found to be 606 mOsm kg^{-1} whereas for the PEG 400-containing orange juice it was 951 mOsm kg^{-1}.

Study Protocol

Ten male volunteers (age range 24–50 years, median 29 years; weight range 63–95 kg, median 76 kg; height range 1.70–1.96 m, median 1.76 m) participated in the study after providing written informed consent. All declared themselves healthy, were non-smokers, were not taking any medication and had no history of gastrointestinal disease. The experimental protocol was separately approved by the Joint UCL/UCLH Committees on the Ethics of Human Research and the Department of Health Administration of Radioactive Substances Advisory Committee (ARSAC). The study was conducted in accordance with the provisions of the declaration of Helsinki (1964) and its subsequent revisions. Two days of study, at least one week apart, were completed by each volunteer. After adherence to an overnight fast, each volunteer received on separate occasions the following treatments in a randomised order: 150 ml of orange juice containing 0 (control) or 10 g of PEG 400 (test). Each volunteer also concurrently received a capsule containing 300 mg of pellets on both occasions. A small sealed point source of 0.5 MBq ^{99m}Tc was taped to the abdominal skin at the most lateral position of the right lower costal margin to act as an anatomical reference marker. Imaging was performed using a double-headed gamma camera (Maxxus, General Electric Medical Systems, Milwaukee, USA) fitted with two opposed detectors, each having a 508 × 368 mm useful field of view and capable of simultaneous data acquisition. Each detector was fitted with a medium energy parallel hole collimator suitable for both ^{99m}Tc and ^{111}In imaging. At 0900 h on the day of the study the volunteer received the capsule and one or other of the orange juice preparations, and was then positioned supine between the two detectors of the gamma camera. Simultaneous anterior and posterior images of 30 s duration were acquired for each radionuclide in turn every 5 min until both preparations had emptied from the stomach. Thereafter, images were acquired at 10–15 min intervals. In between image acquisitions, the volunteer was free to move away from the camera. A standard lunch was provided 4 h post dose, and water and other non-alcoholic drinks were available ad libitum from this point onwards. Images were digitally recorded using an integrated computer system (Starcam 3200i, General Electric Medical Systems, Milwaukee, USA) and archived onto optical disk for later analysis.

Data Analysis

Processing of image data was performed using a Hermes image processing workstation (Nuclear Diagnostics, Stockholm, Sweden). The series of ^{111}In liquid and ^{99m}Tc pellet images acquired for each volunteer was replayed on the computer system. Three regions of interest were highlighted on the computer screen by cursor, representing the stomach, caecum/colon and anatomical marker. The full sequence of images was viewed to check for movement of the volunteer by referring to the anatomical marker. Any volunteer movement was then corrected using a proprietary motion correction package (Nuclear Diagnostics, Stockholm, Sweden). The counts recorded for each region of interest by each detector were calculated by the computer for each image. These values were corrected for background count rates by subtracting from each pixel in the region of interest, the mean counts per pixel from a region at the edge of each image. Administration of both ^{99m}Tc and ^{111}In together leads to some of the scattered radiation, emitted from the higher energy radionuclide, being accepted within the energy window of the lower energy radionuclide, ^{99m}Tc (down-scatter). To compensate for this, correction factors for down-scatter were derived from a series of *in vitro* phantom studies acquired under the same imaging conditions and applied to the data set. To correct for differential attenuation of the radiation with varying depth of source, the geometric mean of the anterior and posterior counts was calculated (4). These counts were then corrected for physical decay of the radionuclide. Finally, the corrected geometric mean counts for the regions of interest were expressed as percentages of the total counts recorded initially when all the administered activity was in the stomach region. The time course of gastric emptying and caecum/colon arrival could then be estimated from the plot of percentage activity in these regions versus time.

The gastrointestinal transit data were quantitatively assessed using statistical moments to calculate the mean gastric residence time (MGRT) and mean caecum arrival time (MCAT) (5). These parameters provide a better single point indicator of the gastric emptying and caecum/colon arrival processes than other descriptors such as the $t_{50\%}$ measure. The principles behind the computation of these statistical parameters and their advantages over other approaches to characterise gastrointestinal transit are documented in detail elsewhere (5). The difference between the MGRT and MCAT represents the mean small intestinal transit time (MSITT).

Statistical analysis by way of a paired Student's t-test was performed on the MGRT, MCAT, and MSITT data for the liquid and pellet preparations to assess the effect of PEG 400 on transit.

RESULTS AND DISCUSSION

The mean gastric residence (MGRT), mean small intestinal transit (MSITT) and mean caecum arrival times (MCAT) for the liquid and pellet preparations in each individual are presented in Tables I and II, respectively.

Liquid emptying was consistently and equally rapid in all volunteers, irrespective of the nature of the liquid preparation (mean MGRT of 20 min for both the control and test preparations). The slight difference in volume administered and osmolality of the two preparations by virtue of the presence of PEG 400 therefore had no significant effect on the liquid gastric emptying rate ($p = 0.948$). The shape of the profiles suggested that the liquids were emptying according to a first-order process. The proximal region of the stomach is primar-

Table I. Gastrointestinal Liquid Transit Parameters

	Mean gastric residence time (MGRT) (min)		Mean small intestinal transit time (MSITT) (min)		Mean caecum arrival time (MCAT) (min)	
Volunteer	Control[a]	Test[b]	Control	Test	Control	Test
1	17	18	200	144	217	162
2	13	19	250	169	263	188
3	30	10	227	138	257	148
4	17	23	256	128	273	151
5	36	31	212	190	248	221
6	23	25	197	138	220	163
7	13	15	197	133	210	148
8	30	19	297	271	327	290
9	13	18	320	137	333	155
10	11	23	204	85	215	108
Mean	20	20	236	153	256	173
s.d.	9	6	44	49	45	50
P value	0.948		<0.001		<0.001	

[a] Control = orange juice preparation.
[b] Test = orange juice + PEG 400 preparation.

ily responsible for this emptying pattern (6). Slow sustained low amplitude contractions in the proximal region of the stomach generate a small pressure gradient between the gastric cavity and duodenum, causing flow of liquid into the duodenum (7).

Pellet emptying was more variable and complex in nature, and generally occurred after liquid emptying. As with liquid emptying, the presence of PEG 400 had no significant effect on the gastric emptying of pellets (mean MGRT of 42 min for the control vs. mean MGRT of 56 min for the test preparation, $P = 0.244$). On occasions, the pellets emptied as a series of small boluses. On other occasions, however, emptying occurred as a few large boluses and was complete within a short period of time. These observations are well-documented (3,8) and can in part be attributed to the migrating myoelectric complex (MMC). The MMC, which lasts for about 2 h, can be divided into four separate stages or phases of activity in the fasted state (9,10). In particular, phase III of the MMC, also known as the 'housekeeper wave', consists of a short period of intense contractions migrating distally from the stomach to the colon, which are powerful enough to clear the gastric lumen of cellular debris and indigestible substances. The pellets in this study are non-disintegrating and will therefore be treated by the stomach as indigestible and hence empty mainly during phase III of the MMC. These pellets may also empty, albeit at a slower rate, during the other more quiescent and less intense phases of the fasting motility cycle, as long as the contractions generated during these phases are sufficiently powerful to propel the pellets through the pylorus. Pellets, by virtue of their small size and mass, are more likely to empty under these non-phase III conditions than large non-disintegrating tablets or capsules.

After emptying from the stomach, the liquid and pellet preparations were observed to transit at different rates

Table II. Gastrointestinal Pellet Transit Parameters

	Mean gastric residence time (MGRT) (min)		Mean small intestinal transit time (MSITT) (min)		Mean caecum arrival time (MCAT) (min)	
Volunteer	Control[a]	Test[b]	Control	Test	Control	Test
1	40	47	225	209	265	256
2	19	42	255	296	274	338
3	61	16	289	170	350	186
4	11	109	251	273	262	382
5	50	50	234	167	284	217
6	56	61	236	160	292	221
7	33	25	206	241	239	266
8	55	71	356	196	411	267
9	42	90	308	253	350	343
10	48	52	194	165	242	217
Mean	42	56	255	213	297	269
s.d.	16	28	49	50	56	65
P value	0.244		0.074		0.347	

[a] Control = orange juice preparation.
[b] Test = orange juice + PEG 400 preparation.

through the remainder of the gastrointestinal tract, often with a period of accumulation and stagnation at the ileocaecal junction prior to bolus entry into the caecum and passage through the colon. The caecum arrival times for the two liquid preparations were significantly different (mean MCAT of 256 min for the control vs. mean MCAT of 173 min for the test preparation, $P < 0.001$). Since the gastric emptying times for the preparations were virtually identical (mean MGRT of 20 min for both preparations), differential rates of transit through the small intestine was responsible for the disparate caecum arrival times. This effect can be attributed to PEG 400. The mean small intestinal transit time for the control preparation was 236 min, which is in agreement with values reported in the literature (11). The corresponding value for the PEG 400-containing liquid formulation was markedly lower at 153 min. These results clearly demonstrate that PEG 400 has a statistically significant effect on small intestinal transit, resulting in a 35% reduction in liquid transit time ($p < 0.001$). The reason for this transit effect is probably related to the fact that PEG 400 is incompletely absorbed from the gastrointestinal tract. Chadwick *et al.* (12) have shown that 34% of a 10 g oral dose of PEG 400 is unabsorbed from the gut and excreted unchanged in the faeces. Urinary recovery has been reported to vary between 14 to 59% of the dose administered (12,13). The hypertonic PEG 400-containing liquid preparation administered in the present study, on emptying from the stomach, will be rapidly neutralised by the secretion of fluid into the lumen of the intestine. Moreover, the osmotic activity of unabsorbed PEG 400 within the intestine will be offset by the retention of fluid in the lumen. This net secretion and inhibition of absorption of fluid will therefore increase the bulk fluid volume in the gut, which in turn will stimulate peristalsis and hence hasten transit through the small intestine. Along similar lines, the excipients sodium acid pyrophosphate and mannitol at concentrations relevant to pharmaceutical formulation have also been shown to have an accelerating effect on small intestinal transit (14–16).

In accord with the reduction in small intestinal liquid transit observed in this study, it would be reasonable to assume that PEG 400 would also have an effect on the transit of the pellets. Although small intestinal pellet transit in the presence of PEG 400 was slightly shorter (mean MSITT = 213 min) than in the absence of PEG 400 (mean MSITT = 255 min), the effect was not statistically significant ($p = 0.074$). These mean values are in agreement with those previously reported for small intestinal transit of pellet dosage forms (3,11). The reason for the lack of effect of PEG 400 on pellet transit may be due to the fact that the pellets were generally retained in the stomach for longer periods of time than the liquid. In all likelihood, the liquid would therefore progress sufficiently ahead of the pellets in the small intestine to impart little or no influence on the transit of the proceeding pellets. Any pellets, however, that concurrently emptied with the PEG 400-containing liquid would be transported through the small intestine at an accelerated rate and give rise to a reduced intestinal transit time. This may explain why small intestinal pellet transit was shorter, although not to any significant effect, in the presence of PEG 400.

Although the effect of PEG 400 on intestinal transit was quite untoward, higher molecular weight PEGs, such as PEG 3350, are routinely administered for this purpose (17–19). PEG 3350 is commercially available in powder form as an osmotic laxative for the treatment of constipation (Movicol in the UK). Moreover, bowel-cleansing preparations based on higher doses of PEG 3350 are also available for the purpose of bowel evacuation prior to colonic endoscopy or surgery (Klean-Prep in the UK). This preparation, once reconstituted, contains 240 g of PEG 3350, and a series of electrolytes, dissolved in 4 litres of water, and is administered over a 4 h period for a rapid cathartic effect on bowel contents. Given that PEG 3350 is virtually non-absorbable from the gastrointestinal tract (19,20) and that large quantities of the polymer are administered in these situations it is not unduly surprising that it has a major osmotic and hence transit effect in the gut. However, somewhat surprisingly this study has shown that PEG 400, a more absorbable form of PEG than PEG 3350, administered at a dose well below the therapeutic doses of PEG 3350 also has a major effect on small intestinal transit. This transit effect did not manifest itself into enhanced bowel evacuation as none of the volunteers reported suffering from diarrhoea as a result of the study.

The small intestine is well known to be the primary site of drug absorption within the gastrointestinal tract. Furthermore, it is expected that the extent of absorption and bioavailability of a drug is related to its residence time within this region of the gut. For those drugs that are predominantly absorbed from the small intestine, any change in the rate at which the drug moves through this section of the gut is liable to alter its extent of absorption. On the other hand, drugs that are absorbed throughout the gastrointestinal tract are less likely to be influenced, in terms of extent of absorption, by changes in transit, although the rate of absorption may be affected. PEG 400, by means of reducing residence time in the small intestine, is therefore likely to have a detrimental effect on the rate and/or extent of absorption of drugs.

Overall, these findings have important consequences with regard to the formulation of poorly water-soluble drugs with PEG 400. The use of PEG 400 will not only improve the solubility of such drugs, but the concurrent reduction in gastrointestinal transit time, specifically small intestinal transit, may limit the opportunity for drug absorption and nullify any possible bioavailability enhancement. In summary, therefore, PEG 400 cannot be considered an inert pharmaceutical excipient.

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