JPP Journal of Pharmacy and Pharmacology

JPP 2006, 58: 821–825

Received October 4, 2005
Accepted February 26, 2006
DOI 10.1211/jpp.58.6.0012
ISSN 0022-3573

Impact of formulation excipients on human intestinal transit

Julia D. R. Schulze, Diane A. I. Ashiru, Mandeep K. Khela, David F. Evans, Rajesh Patel, Gary E. Parsons, Mark D. Coffin and Abdul W. Basit

Abstract

The accelerating effect of polyethylene glycol 400 on small intestinal transit has been previously reported. The aim of this study was to investigate the influence of other solubility-enhancing excipient, propylene glycol, D-α-tocopheryl-polyethylene glycol-1000 succinate (VitE-TPGS) and Capmul MCM, on human intestinal transit. A 5-g dose of each excipient was administered to seven healthy male subjects. Propylene glycol and VitE-TPGS were administered dissolved in 150 mL water. Capmul MCM was administered in the form of four 000 hard gelatin capsules to mask its taste and then given with 150 mL water. On a separate occasion, 150 mL water was administered as the control. Each formulation was radiolabelled with technetium-99 m to follow its transit using a gamma camera. The mean small intestinal transit times were 234, 207, 241 and 209 min for the control, propylene glycol, VitE-TPGS and Capmul MCM treatments, respectively. Although there were differences in the small intestinal transit times for the excipients investigated compared with the control, none of the results were statistically significant. Unlike polyethylene glycol 400 at the same dose of 5 g, the excipients tested (propylene glycol, VitE-TPGS and Capmul MCM) had little or no impact on small intestinal transit.

Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK

Julia D. R. Schulze*, Diane A. I. Ashiru, Abdul W. Basit

The Wingate Institute, Queen Mary College, University of London, London, UK

Mandeep K. Khela, David F. Evans

GlaxoSmithKline, Harlow, Essex, UK

Rajesh Patel

GlaxoSmithKline, Ware, Hertfordshire, UK

Gary E. Parsons

GlaxoSmithKline, Research Triangle Park, North Carolina, USA

Mark D. Coffin

Correspondence: A. W. Basit, Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK. E-mail: abdul.basit@pharmacy.ac.uk

Acknowledgements and funding: Julia D. R. Schulze gratefully acknowledges GlaxoSmithKline (formerly GlaxoWellcome) for the award of a studentship. Diane A. I. Ashiru gratefully acknowledges the Medical Research Council (MRC) and GlaxoSmithKline for the award of a studentship.

***Current address:** Schering AG, Muellerstrasse 178, 13342 Berlin, Germany.

Introduction

The oral route remains the most common and acceptable method of administering drugs – over 85% of the 100 most-prescribed pharmaceutical products in the UK and USA are oral medications (Department of Health 2004; RxList 2004). Solubility is an important factor that influences the bioavailability of oral medications. Drug solubility can be increased by the addition of solubilizing excipients such as co-solvents, surfactants, complexing agents and pH modifiers (Strickley 2004).

For many years it was assumed that pharmaceutical excipients were inert and that their role in bioavailability was linked simply to their physicochemical role (e.g. solubilization). In recent years, the notion that excipients are inert has been challenged. It is well known that excipients are indeed capable of increasing the bioavailability of drugs by increasing their solubility in physiological fluids of the gastrointestinal tract. However, recent research has shown that excipients may have a detrimental effect on drug bioavailability (Koch et al 1993; Adkin et al 1995a; Basit et al 2002). Sodium acid pyrophosphate (SAPP), an excipient selected for developing an effervescent solution of ranitidine, was found to decrease the absorption of ranitidine by nearly 50% when compared with solutions not containing SAPP (Koch et al 1993). The authors suggested that the decrease was likely to be due to SAPP causing a significant decrease in small intestinal transit time (56%) (Koch et al 1993). Other excipients, such as xylitol (Wilding et al 1994), mannitol (Adkin et al 1995b) and polyethylene glycol 400 (PEG 400) (Basit et al 2001), have also been implicated in reducing small intestinal transit time in man. There have been reports that the bioavailability of drugs such as griseofulvin and etoricoxib is reduced when formulated in PEG 400 as liquid formulations compared with conventional solid formulations (Hansford et al 1980; Rodrigues et al 2003). Although not investigated by the authors, it is possible that the reduction in

the bioavailability of these drugs when administered as oral solutions is due to the transit effects of PEG 400.

The concentration-dependent effects of PEG 400 on intestinal transit and drug bioavailability were investigated by Schulze et al (2003). In general, it was found that increasing the concentration of the excipient led to an increased acceleration of small intestinal transit and subsequently a decreased bioavailability of the model drug ranitidine (Basit et al 2002; Schulze et al 2003). The doses of PEG 400 tested (1, 2.5, 5 and 10 g) reduced intestinal transit time by 9, 20, 23 and 37%, respectively. The bioavailability of ranitidine decreased by up to 38% in the presence of the higher doses of PEG 400 (2.5, 5 and 10 g) (Basit et al 2002; Schulze et al 2003). However, surprisingly, in the presence of 1 g PEG 400, the bioavailability of ranitidine increased by 48% (Schulze et al 2003).

In light of these intriguing results, the main objective of this study was to investigate whether other types of excipients, which are commonly used in solution and soft gelatin capsule preparations, affect small intestinal transit in a similar way to PEG 400. The cosolvent propylene glycol and the surfactants D-α-tocopheryl polyethylene glycol 1000 succinate (VitE-TPGS) and Capmul MCM were investigated for their impact on small intestinal transit using the non-invasive technique of gamma scintigraphy.

Materials and Methods

Dosage forms

Propylene glycol (Sigma-Aldrich, Poole, UK) is a low-molecular-weight (MW 76), water-soluble cosolvent. VitE-TPGS (Eastman Chemical, TN, USA), a waxy solid, is a non-ionic water-soluble surfactant (MW 1513). It is prepared by the esterification of the acid group of crystalline D-α-tocopheryl acid succinate with polyethelene glycol 1000. Capmul MCM (Abitec Corp., WI, USA) consists of mixtures of mono-, di- and triglycerides of medium-chain fatty acids, mainly caprylic and capric acid (MW approx. 500) and it is therefore often referred to as a medium-chain glyceride.

Each excipient was administered at a dose of 5 g in 150 mL water. However, for Capmul MCM, the 5-g dose was divided and filled in a total of four 000 hard gelatin capsules. This was necessary to mask the unpleasant taste of Capmul MCM. The other excipients were administered directly in 150 mL of water to allow consistency with our other studies on excipient effects (Schulze et al 2003), thus allowing more robust comparison between studies. The waxy surfactant VitE-TPGS was heated in an oven at 37°C to melt it before adding 5 g of the liquefied surfactant to water for administration. The mixture was stirred at approximately 60°C until complete dissolution of VitE-TPGS and then cooled to room temperature. Propylene glycol was added directly to the water. The control was 150 mL water.

The osmotic pressure of the drug solutions was measured by freezing-point depression with a digital micro-osmometer (Type 5R; Roebling, Germany). Each solution was placed in a 100-μL sample tube as required by the osmometer. For propylene glycol, the solution was diluted (1:10) to achieve freezing. The osmolality of the ingested fluid was 4 mOsm kg^{-1} (control), 508 mOsm kg^{-1} (propylene glycol), 22 mOsm kg^{-1} (VitE-TPGS) and 39 mOsm kg^{-1} (Capmul MCM).

Study protocol

Seven male subjects (age range 24–48 years, median 28 years; weight range 61–89 kg, median 76 kg; height range 1.68–1.86 m, median 1.78 m) participated in an open four-way crossover study, after giving written informed consent. All subjects were non-smokers, declared themselves healthy and had no history of gastrointestinal disease.

The experimental protocol was approved by the East London and The City Health Authority Ethics Committee. Authority was obtained from the Administration of Radioactive Substances Advisory Committee at the Department of Health to administer radiopharmaceuticals. The study was conducted in accordance to the Helsinki guidelines for ethics in research (1965) and its subsequent revisions.

The different treatments, all radiolabelled with 7 MBq of technetium-99 m (^{99m}Tc-DTPA) included: Control – 150 mL water; Propylene glycol – 5 g propylene glycol in 150 mL water; VitE-TPGS – 5 g VitE-TPGS in 150 mL water; and Capmul MCM – 5 g, administered in the form of four 000 hard gelatin capsules and given with 150 mL water.

The subjects reported to the study centre after an overnight fast. A small sealed point source of 0.5 MBq ^{99m}Tc was taped to the abdominal skin at the position of the right lower costal margin of each subject to act as an abdominal reference marker.

Imaging was conducted using a single-headed General Electric Maxicamera 400AC (400T; Milwaukee, USA). The detector had a 40-cm diameter field of view and was fitted with a low energy parallel hole collimator suitable for ^{99m}Tc imaging. An on-line computer (Sun Workstation; Sun Microsystems, Milwaukee, USA) was connected to the camera for digital image recording. Data was archived onto CD and hard drive to enable subsequent analysis.

After oral administration of the appropriate formulation, the subject was positioned upright standing in front of the detector head, facing the gamma camera for the anterior image of 30-s duration. The subject was then immediately repositioned with their back facing the detector head to acquire the posterior image, also of 30-s duration. The anterior and posterior images were acquired at time zero and then every 5 min for the first 30 min, followed by every 10 min until lunch and finally every 15 min after lunch until all the activity had accumulated in the colon. Between

image acquisitions, the subject was free to move away from the camera, but was requested to remain in an upright position. A standardized lunch consisting of a two-piece cheese sandwich, packet of crisps and orange juice was provided 4 h post dosing; water and orange juice were freely available following lunch.

Scintigraphic data analysis

Image data was processed using customized computer software (MicasV Nucmed software; Park Medical Systems, Farnborough, UK). Regions of interest (ROI) were drawn to highlight the stomach, colon and anatomic markers. The counts of radioactivity were calculated in each ROI of the stomach and colon after correcting for movement of the subjects, background radiation and physical decay of ^{99m}Tc. From the net counts, the geometric mean was calculated to account for the differential attenuation of the radiation with varying depth of source. Finally, the corrected geometric mean counts for the ROI were expressed as percentages of the total counts recorded initially when all the administered activity was in the stomach and terminally when all the activity was in the caecum/colon. The time course of gastric emptying and colon arrival was calculated from the plot of percentage activity in these regions versus time.

The gastrointestinal transit data were quantitatively assessed using statistical moments to calculate mean gastric residence time (MGRT) and mean caecum/colon arrival time (MCAT) for the different treatments (Podczeck et al 1995); the difference between MGRT and MCAT provides a measure of mean small intestinal transit time (MSITT).

Statistical analysis

Using SPSS software, one-way analysis of variance was performed on the scinitigraphic data to assess the effects of the different excipients on gastrointestinal transit. This was followed by a post-hoc Tukey's test to determine whether observed differences in results were statistically significant.

Results and Discussion

The mean gastric emptying times for all formulations are shown in Table 1. Mean gastric emptying time for the control formulation was 11 min. In the presence of propylene glycol, the mean gastric emptying was also 11 min and the corresponding mean time for VitE-TPGS was 14 min. These gastric emptying times were not significantly different from the control and are in general agreement with literature data (Schulze et al 2003). In the presence of Capmul MCM, there was a significant increase in gastric emptying time (25 min), suggesting that Capmul MCM delays gastric emptying by more than 2-fold in man. However, it should be appreciated that Capmul MCM was administered in the form of capsules (to mask its unpleasant taste) and not directly in water and this would have influenced the overall gastric emptying results. Visual examination of the scintigraphic images indicated that the Capmul MCM-containing capsules had disintegrated between the second and third image acquisitions (5–10 min) in all subjects. This agrees with literature data; hard gelatin capsules such as those used in this study have been shown to disintegrate within 10 min (Tuleu et al 2002) and in another study the mean disintegration time was reported as 7 min (Digenis et al 2000). If the disintegration time for the capsules (assuming a mean time of 7 min) is subtracted from the gastric emptying times, the overall emptying trend for the Capmul MCM treatment is no longer statistically significant.

Table 1 Gastric emptying times calculated using statistical moment theory and represented as mean gastric residence time, MGRT (min)

Treatment	Subject							Mean ± s.d.
	1	2	3	4	5	6	7	
Control	23	7	18	17	2	9	1	11 ± 8
Propylene glycol	11	18	16	1	14	7	8	11 ± 6
VitE-TPGS	7	15	31	14	18	8	7	14 ± 9
Capmul MCM	18	13	48	30	30	18	21	25 ± 12

Table 2 shows the colonic arrival times. On average, arrival of the formulations in the colon was 245, 217, 255 and 235 min for the control, propylene glycol, VitE-TPGS and Capmul MCM, respectively. None of the colonic arrival times for the excipients were significantly different to the colonic arrival time for the control.

The small intestinal transit times are shown in Table 3. The average transit time for the control formulation was 234 min. This is in agreement with literature data (Davis et al 1986). The mean small intestinal times for propylene glycol, VitE-TPGS and Capmul MCM preparations were

Table 2 Caecum arrival times calculated using statistical moment theory and represented as mean caecum arrival time, MCAT (min)

Treatment	Subject							Mean ± s.d.
	1	2	3	4	5	6	7	
Control	279	239	299	207	187	256	245	245 ± 39
Propylene glycol	270	228	190	194	227	187	225	217 ± 30
VitE-TPGS	249	251	304	244	238	247	251	255 ± 22
Capmul MCM	223	173	453	168	173	258	194	235 ± 102

Table 3 Small intestinal transit times (MSITT) calculated using statistical moment theory and represented as the difference between MGRT and MCAT (min)

Treatment	Subject							Mean ± s.d.
	1	2	3	4	5	6	7	
Control	256	232	281	190	185	247	244	234 ± 35
Propylene glycol	259	210	174	193	213	180	217	207 ± 28
VitE-TPGS	242	236	273	230	220	239	244	241 ± 16
Capmul MCM	205	160	405	138	143	240	173	209 ± 94

207, 241 and 209 min, respectively. Although propylene glycol and Capmul MCM led to faster transit through the small intestine – a mean 12% and 11% reduction in transit times, respectively – the values were not significantly different from the result obtained for the control formulation. There was little difference in small intestinal transit time for VitE-TPGS compared with the control. Little or no transit effect was also observed with some of these excipients in a previous study using Beagle dogs, although the excipient doses administered to the dogs were much lower (Schulze et al 2005).

The results from this investigation are in marked contrast to those obtained from our previous findings in man with PEG 400 (Basit et al 2001, 2002; Schulze et al 2003). A possible explanation for this difference could be related, in part, to whether an excipient remains in the gut lumen after administration. PEG 400 is osmotically active and poorly absorbed from the gut. Unabsorbed PEG 400 holds fluid in the gut to neutralize its osmotic pressure, this in turn increases the bulk volume in the gut lumen, stimulates peristalsis and accelerates transit. However, unlike PEG 400, propylene glycol (MW 76) is a short-chain alcohol and is probably rapidly absorbed from the intestine; this may explain the lack of transit effect with this excipient.

The absorption characteristics of VitE-TPGS (MW 1513) are not yet well understood. VitE-TPGS consists of polyethylene glycol 1000, a higher-molecular-weight analogue of PEG 400, linked via a succinate bridge to vitamin E. This large-molecular-weight excipient would be expected to be poorly absorbed from the gastrointestinal tract and hence impact on transit, although in-vitro studies suggest that VitE-TPGS enters Caco-2 cells intact before undergoing ester hydrolysis inside the cell (Traber et al 1988). However, it is unclear if this process is quantitative or if partial hydrolysis occurs inside the lumen to release PEG 1000.

There is a possibility that the lack of significant effect with Capmul MCM, a medium-chain triglyceride (MCT) with an approximate molecular weight of 500, may be due to it being digested by human gastric lipase in the stomach. Investigation into gastric lipolysis and fat absorption in infants showed that medium-chain fatty acids are absorbed directly in the stomach (Hamosh et al 1989). If, however, for any reason, digestion of oral medium-chain triglycerides is not completed in the stomach of some individuals, some of the ingested MCT will reach the small intestine. Then there is a possibility of small intestinal transit time being shortened since intraduodenally administered MCTs, compared with long-chain triglycerides, have been shown to significantly accelerate duodenocaecal transit time in healthy human subjects (Verkijk et al 1997).

While the physicochemical properties of these excipients may be indicated in their lack of effect on small intestinal transit, it is also feasible that a 5-g dose of these excipients, unlike PEG 400, is too low to trigger an effect on transit.

Although the results obtained for small intestinal transit for these excipients were not statistically significant, they may have clinical implications – a case in point being the formulations of amprenavir (Agenerase). Amprenavir is a protease inhibitor used in the treatment of HIV infection. It is classified as a class II compound of the BCS (Biopharmaceutics Classification System) (i.e. has poor solubility but good intestinal permeability). It is available on the market as both an oral solution and soft gelatin capsule formulation, although the two preparations are not bioequivalent. The solution has a 14% lower bioavailability than the soft gelatin capsule formulation (Physician's Desk Reference 2004). A single adult dose of the capsule formulation (1200 mg) contains 5.9 g PEG 400, 0.45 g propylene glycol and 3.14 g VitE-TPGS while the equivalent oral solution dose (1400 mg) contains 15.9 g PEG 400, 51.3 g propylene glycol and 1.9 g VitE-TPGS (Physician's Desk Reference 2004). While the disparity in bioavailability between the formulations could be due to differences in terms of drug solubility, release or precipitation from the respective vehicles, transit effects of the excipients may also play a role. For instance, 10 g of PEG 400 reduced small intestinal transit time by 37% and subsequently led to a 31% reduction in the bioavailability of ranitidine (Basit et al 2002). There are significantly higher levels of PEG 400 in the solution formulation of amprenavir than the capsule. This would lead to faster intestinal transit of the solution formulation and might, in part, explain the reduced bioavailability of the solution formulation of amprenavir. While this study shows no significant effect of propylene glycol on transit, it is unclear what effect a dose in excess of 50 g, as found in the solution of Agenerase, will have on small intestinal transit.

In general, many patients suffer from more than one disease and the majority of patients using Agenerase for instance will also suffer from other conditions that require additional medication. In such cases, the presence of excipients which alter small intestinal transit may not only affect the absorption of the drugs they are formulated in but may also adversely affect the absorption and clinical efficacy of co-administered medicines (poly-pharmacy).

In conclusion, we have shown that, unlike with PEG 400, oral administration of a 5-g dose of propylene glycol, VitE-TPGS and Capmul MCM does not have a significant impact on small intestinal transit.

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