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International Journal of Pharmaceutics 300 (2005) 67–75
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Excipient effects on gastrointestinal transit and drug absorption in beagle dogs

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Received 21 March 2005; received in revised form 16 May 2005; accepted 17 May 2005
Available online 23 June 2005

Abstract

Previous work has shown that polyethylene glycol 400 (PEG 400) has an accelerating effect on gastrointestinal transit and a modulating influence on drug absorption in humans. The aim of this study was to assess the impact of various excipients, PEG 400, propylene glycol, D-α-tocopheryl-polyethylene glycol-1000 succinate (TPGS) and Labrasol on gastrointestinal transit and drug absorption in four beagle dogs using scintigraphy. Each dog received, on five separate occasions, water (control) or a dose of excipient equivalent to 1 g PEG 400, 2 g propylene glycol, 1 g TPGS or 2 g Labrasol dissolved in water and administered in the form of two capsules. The model drugs ampicillin (200 mg) and antipyrine (100 mg) were co-administered in the capsules. The capsule solutions were radiolabelled with technetium-99m to follow their transit using a dual-headed gamma camera, and blood samples were collected to determine drug pharmacokinetics. On a separate occasion, the drugs were dissolved in saline and given intravenously. The capsules rapidly disintegrated in the stomach liberating their liquid contents. The mean small intestinal transit times for the different treatments (control, PEG 400, propylene glycol, TPGS and Labarasol) were 183, 179, 195, 168 and 154 min, respectively. The corresponding mean absolute oral bioavailability figures were 36, 32, 39, 42 and 32% for ampicillin and 76, 74, 85, 73 and 74% for antipyrine, respectively. The transit and bioavailability data for the excipient treatments were not significantly different from the control. In summary, these excipients, at the doses administered, have limited influence on gastrointestinal transit and drug absorption in beagle dogs.

Keywords: Excipients; Cosolvent; Gastrointestinal tract; Beagle dogs; Gamma scintigraphy; Polyethylene glycol; Propylene glycol; Vitamin E-TPGS; Labrasol

1. Introduction

The bioavailability of orally administered drugs is in part influenced by their solubility in the physiological

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doi:10.1016/j.ijpharm.2005.05.004

fluids of the gastrointestinal tract. Therefore, adequate aqueous solubility is a prerequisite for drug efficacy via this route. However, many drugs lack this basic attribute and hence provide a challenge for oral delivery. The use of solubility-enhancing excipients offers a potential means of delivering these "difficult" drugs to the body via the gastrointestinal tract. Such excipients include: water-soluble organic solvents, surfactants, medium chain triglycerides, long chain triglycerides, cyclodextrins and phospholipids among others (Strickley, 2004).

The common assumption about excipients is that they are pharmaceutically inert substances, which have no effect on the body. However, we have shown that the cosolvent polyethylene glycol 400 (PEG 400) has a stimulatory effect on gastrointestinal motility and transit in man (Basit et al., 2001, 2002; Schulze et al., 2003). This effect is concentration-dependent, with high doses of PEG 400 (2.5, 5 and 10 g) significantly reducing small intestinal transit time and consequently the time for drug absorption. The bioavailability of the model drug ranitidine was reduced in the presence of these doses. Low doses of PEG 400 (1 g) had less of an influence on transit, but a surprising positive impact on ranitidine bioavailability (Schulze et al., 2003).

The main objective of the present study was to investigate whether other types of excipients commonly employed in solution and soft gelatin capsule preparations modulate transit and drug absorption in a similar way to PEG 400. In addition to PEG 400, the cosolvent propylene glycol and the surfactants D-α-tocopheryl polyethylene glycol 1000-succinate (TPGS) and Labrasol were investigated. These excipients were co-administered with two different transcellular probe compounds, ampicillin and antipyrine. Ampicillin is absorbed in the upper small intestine via an active dipeptide transporter (Lee, 2000), while antipyrine is absorbed throughout the entire intestine through aqueous filled pores (Ungell et al., 1998). While neither of these drugs can be considered poorly water-soluble, they were chosen in part to minimize the likelihood of precipitation from the formulations in the intestine, and hence simplify the interpretation of changes in the pharmacokinetic results in the presence of the excipients.

The present study was conducted in beagle dogs rather than in man. The dog is widely used as an animal model for humans because of its reported similarity in gastrointestinal anatomy and motility, as well as in drug pharmacokinetics. (Anderson, 1970; Dressman, 1986). The use of the canine model is further advantageous in terms of being less expensive and more readily available as well as less time consuming than conducting studies in human volunteers. Dog studies have been used to assess the gastric emptying of meals and the transit of different types of dosage forms through the gastrointestinal tract (Sutton, 2004). A further objective of the present study therefore was to establish whether the canine model is a useful tool to investigate and predict excipient effects in the human gastrointestinal tract.

2. Materials and methods

2.1. Dosage forms

For the oral preparations, 212 mg ampicillin sodium (Sigma, MO, USA), equivalent to 200 mg ampicillin acid, and 100 mg antipyrine (Sigma, MO, USA) were dissolved in 8 g of solvent. The solvent consisted of water (control) or a mixture of either 12.5% (w/w) PEG 400 (Spectrum, NJ, USA), 25% (w/w) propylene glycol (Dow, TX, USA), 12.5% (w/w) TPGS (Eastman, TN, USA) or 25% (w/w) Labrasol® (Gattefossé, NJ, USA) dispersed in water. These concentrations equate to doses of 1, 2, 1 and 2 g, respectively, of excipient present in the preparations. The 1 g dose of PEG 400 was used for comparison purposes with our previous human study (Schulze et al., 2003). Likewise, since TPGS is a PEG-based molecule it was also administered at the same dose (1 g), while the other two excipients were used at higher but equivalent doses (2 g). The PEG 400, propylene glycol and Labrasol formulations were obtained by mixing the respective excipient with water. For the TPGS solution, the waxy surfactant was heated to 37 °C to liquefy the material prior to mixing with water. The solution was then cooled down to room temperature before the drug compounds were added. The drug formulations were filled in two 5 mL Torpac Lock Ring capsules and radiolabelled with technetium-99m (^{99m}Tc) in the form of the complex ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) dissolved in saline (Photon Imaging, NC, USA). The total radioactivity of the solutions in the two capsules was 15 MBq. For the intravenous preparations, 212 mg ampicillin sodium and 100 mg antipyrine were administered dissolved in 4 mL sterile saline solution.

The osmotic pressure of the 8 mL oral drug solutions was measured using a freezing-point osmometer (Model 3D3, Advanced Instruments, MA, USA): control (192 mOsm kg^{-1}); PEG 400 (766 mOsm kg^{-1}); propylene glycol (3784 mOsm kg^{-1}); TPGS (266 mOsm kg^{-1}); Labrasol (631 mOsm kg^{-1}). The pH of the solutions was also measured: control (8.1); PEG 400 (8.2); propylene glycol (7.9); TPGS (8.0); Labrasol (7.9).

2.2. Study protocol

Four beagle dogs (three males and one female) participated in an open six-way crossover study (five oral administrations and one intravenous administration, with a 3 day washout period). The study was approved by the Institutional Animal Care and Use Committee at GlaxoSmithKline. The beagle dogs underwent a 24 h fast on the day prior to each study. On the morning of the day of the oral studies, one fiducial labelled with 1 MBq ^{99m}Tc was placed at the axillary line on either the left or right front shoulder of the dog to serve as anatomical reference marker for the stomach. Imaging was performed using an e.Cam Fixed 180 dual head SPECT camera (Siemens Medical Solutions, PA, USA). The two opposed detectors, each having a 533 mm × 387 mm field of view were fitted with low energy parallel hole collimators suitable for ^{99m}Tc imaging. Dosing of the treatments was performed placing one capsule with approximately 20 mL of water in the mouth, holding the jaws closed until the dog swallowed. The procedure was repeated for the second capsule. The dogs were seated comfortably in a sling under the camera and scintigraphic images of 30 s duration were simultaneously acquired from both anterior and posterior detectors. During the first 30 min images were acquired in a continuous manner until the capsules had disintegrated and their liquid contents emptied from the stomach. Imaging was continued less frequently after gastric emptying at intervals of about 15 min duration until the liquid had arrived at the colon. Between image acquisitions, the dogs were allowed to move freely in the room or were brought back to their cages. Water was made available ad libitum once the drug solution had emptied from the stomach and the dogs were fed their daily standard food (Canine food 5006, LabDiet®, IA, USA) 4 h after dosing. An online computer was connected to the camera and digital image recording was performed using an e.Soft programme (Siemens Medical Solutions). For subsequent analysis data were archived onto CD and hard drive.

In addition to imaging, a cannula was inserted into the cephalic vein of the right or left front leg to allow regular blood sampling. Samples of 5 mL blood were taken at specific times: 0 (pre-dose), 5, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h on the days of oral administration and 0 (pre-dose) 3, 7, 10, 15, 30, 45 min, 1, 1.5, 2, 3, 4 and 6 h after intravenous administration. Blood samples were centrifuged in heparin vials at 10,000 rpm for 5 min and separated plasma was immediately stored at −20 °C prior to analysis.

2.3. Scintigraphic data analysis

On completion of each scintigraphic study, processing of image data was performed using a DICOM image processing software programme (Siemens Medical Solutions). The series of images acquired for each dog was replayed on computer. After correcting the images for motion two regions of interest (ROI) were drawn around the stomach and the colon and radioactivity within these regions was quantitatively assessed for each image. These values were then corrected for background count rates and physical decay of ^{99m}Tc for both anterior and posterior data sets. From these 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 regions of interest 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, to generate curves of gastric emptying and caecum/colon arrival, respectively.

The gastrointestinal transit data were quantitatively assessed using statistical moments to calculate the mean gastric residence time (MGRT) and mean caecum arrival time (MCAT) (Podczeck et al., 1995). The mean small intestinal transit time (MSITT) was the difference between the MGRT and MCAT.

2.4. Plasma analysis

After thawing at room temperature and thorough vortex mixing, the plasma samples were pre-treated for protein precipitation according to Akhtar et al. (1993).

Here, 70 μL of buffered trichloroacetic acid (TCA), consisting of 1:3 (v/v) citrate-phosphate buffer (pH 5.5) and 70% (w/v) (TCA), was added to 0.7 mL of plasma. The mixture was vortex mixed for 30 s and centrifuged at 4000 rpm for 5 min (5415C, Eppendorf, Germany). From the supernatant 0.4 mL was transferred into an HPLC vial containing 10 μL of 5 M sodium hydroxide, which was then sonicated in an ultrasonic water bath for 10 s.

The HPLC analysis utilized a Hewlett Packard Series 1100 chromatography system with a CTC PAL autosampler. Aliquots of sample (150 μL) were injected on a 100 mm × 4.6 mm Luna column (3 μm C-18(2); Phenomenex, CA, USA) at 40 °C. A binary solvent gradient system was used and the flow rate of the mobile phase was set to 1.0 mL/min. The mobile phase comprised of an aqueous and an organic solvent, which were 0.05% (v/v) trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B), respectively. The column was initially equilibrated with 95% solvent A and 5% solvent B. Immediately after sample injection, the concentration of B was linearly increased over 15 min to a concentration of 30% and then reduced to the initial concentration of 5% in the next 3 min followed by a 1 min equilibration time before the next sample injection. The retention times of ampicillin and antipyrine were 8.8 and 9.5 min, respectively.

Plasma ampicillin and antipyrine concentration time profiles were constructed for the oral treatments in each individual dog. The maximum plasma drug concentration (C_{max}) and time to C_{max} (T_{max}) were read directly from the curves. The area under the plasma curve to the last time point ($AUC_{0\text{-}12}$) and extrapolated to infinity ($AUC_{0\text{-}inf}$) for the oral and intravenous administrations were calculated using WinNonLin (Pharsight Corporation, Mountains View, USA). The absolute bioavailability of each treatment was calculated by dividing the $AUC_{0\text{-}inf}$ obtained after oral administration with the $AUC_{0\text{-}inf}$ obtained after intravenous administration.

2.5. Statistical analysis

A paired Student's *t*-test was performed on the scintigraphic and pharmacokinetic data to assess the impact of the excipients on gastrointestinal transit and drug absorption.

3. Results and discussion

3.1. Excipient effects on gastrointestinal transit

After oral administration the capsules disintegrated rapidly in the stomach releasing their liquid contents. The results for the mean gastric residence time (MGRT) of the different formulations are presented in Table 1. The average MGRT for the control formulation was 30 min, which agrees well with values reported in the literature for emptying half times in dogs (Dressman, 1986; Gupta and Robinson, 1988). The corresponding mean MGRTs for the PEG 400, propylene glycol, TPGS and Labrasol treatments were 30, 27, 38 and 33 min, respectively, suggesting that the nature of the formulation does not influence emptying. Ingestion of fluid volumes up to 100 mL such as in the present study does not interrupt the fasting motility pattern in the stomach (Gupta and Robinson, 1988). The emptying time of these liquids is therefore partly dependent on the state of the fasting cycle at the time of dosing. This is reflected in the variability in the MGRTs of the individual dogs. Dosing during Phase I or II of the myoelectric motor complex (MMC) leads to an emptying pattern from the stomach which is typically slow and continuous, whereas administration during Phase III of

Table 1
Gastric emptying times calculated using statistical moment theory and represented as MGRT (min)

Treatment	Dog				Mean ± S.D.	*P*-value
	One	Two	Three	Four		
Control	41	9	39	31	30 ± 15	
PEG 400	47	3	21	47	30 ± 22	0.950
Propylene glycol	38	10	35	25	27 ± 13	0.143
Vitamin E-TPGS	34	40	28	49	38 ± 9	0.497
Labrasol	24	25	36	48	33 ± 11	0.717

Table 2
Caecum arrival times calculated using statistical moment theory and represented as MCAT

Treatment	Dog				Mean ± S.D.	*P*-value
	One	Two	Three	Four		
Control	164	280	196	212	213 ± 49	
PEG 400	203	134	201	296	209 ± 67	0.934
Propylene glycol	155	226	259	247	222 ± 47	0.755
Vitamin E-TPGS	163	207	203	251	206 ± 36	0.786
Labrasol	145	179	174	249	187 ± 44	0.423

the MMC results in abrupt gastric emptying, which is reflected in an exponential pattern.

The mean caecum arrival time (MCAT) and mean small intestinal transit time (MSITT) for the different preparations are presented in Tables 2 and 3, respectively. The mean MSITT for the control treatment was 183 min, which is in agreement with previously reported small intestinal transit times in canines (Dressman, 1986). In the presence of PEG 400, propylene glycol, TPGS and Labrasol, the mean MSITTs were 179, 195, 171 and 154 min, respectively. Although different, these figures were not significantly different to the control.

In man, PEG 400 has been shown to accelerate small intestinal transit in a concentration-dependent manner (Basit et al., 2001; Schulze et al., 2003). High doses of PEG 400 (2.5–10 g) significantly reduced the MSITT, whereas 1 g of the polymer resulted in a non-significant reduction in the MSITT of 9%. The results of the present canine study, therefore, appear to correlate with the earlier findings in humans. In man, the mechanism behind the transit effect of PEG 400 is related to the polymer's osmotic activity and incomplete absorption from the human small intestine. PEG 400 increases the luminal fluid volume via the retention of water, which in turn stimulates motility and hence transit. In comparison to the human gut, the intestinal epithelium of the dog is more permeable to hydrophilic compounds because of the larger size and frequency of pores in the canine paracellular route (He et al., 1998). He et al. (1998) investigated the permeability of polyethylene glycols of various molecular weights and found quantitative absorption for oligomers up to 600 Da. It is therefore feasible that in the present study PEG 400, consisting of ethylene glycol oligomers with a molecular weight range from 238 to 594 Da, is extensively absorbed from the dog small intestine, leaving little behind in the lumen to have an effect on transit.

The chemical structure of TPGS comprises a linkage of Vitamin E via a succinate bridge to polyethylene glycol 1000 (PEG 1000), a polymer similar to PEG 400 with an average molecular weight of 1000 Da. The administration of 1 g TPGS resulted in no significant transit alterations compared to the control. The mechanism of absorption of TPGS is not yet fully understood. Although linkage to the high molecular weight PEG would suggest poor absorption from the GI tract, an in vitro study using Caco-2 cells revealed that TPGS enters the cells intact undergoing ester hydrolysis inside the cell (Traber et al., 1988). It is, however, unclear whether this process occurs quantitatively or whether partial ester hydrolysis takes place inside the lumen releasing PEG 1000. It has, therefore, yet to be

Table 3
Small intestinal transit times (MSITT) calculated as the difference between MGRT and MCAT (min)

Treatment	Dog				Mean ± S.D.	*P*-value
	One	Two	Three	Four		
Control	123	271	157	181	183 ± 63	
PEG 400	154	131	180	249	179 ± 51	0.929
Propylene glycol	117	216	224	222	195 ± 52	0.692
Vitamin E-TPGS	129	167	175	202	168 ± 30	0.656
Labrasol	121	154	138	201	154 ± 34	0.401

established whether higher concentrations TPGS may exert an effect on small intestinal transit.

In the presence of 2 g propylene glycol no significant effect on small intestinal transit was observed. On ingestion, the hypertonic cosolvent preparation (3784 mOsm kg^{-1}) is expected to face immediate dilution by secretion of water. However, as a low molecular weight alcohol propylene glycol is rapidly and extensively absorbed from the upper small intestine, which could explain its lack of effect on transit.

Labrasol, a mixture of medium chain glycerides, was expected to increase the MSITTs as a result of the luminal presence of fat digestion products. Upon release in the stomach, Labrasol is immediately hydrolysed by gastric lipase as well as the pancreatic lipase/colipase complex (Sek et al., 2002) releasing free fatty acids, caprylic (C_8) and capric acids (C_{10}), predominantly. Fatty acids inside the intestinal lumen have been shown to activate the duodenal or ileal braking mechanism causing a slowing in the passage of the luminal contents (Dobson et al., 1999), an effect, which has also been shown to occur in dogs (Dresznik et al., 1994). However, in the present study, a decrease rather than an increase in the MSITT was observed. In general, the reported literature has shown a high variability between subjects, and high amounts of brake-activators were necessary to elicit an effect (Dobson et al., 1999, 2000). It is therefore likely that the administered amount of Labrasol was not sufficient to elicit a slowing effect on the passage of the administered solution.

3.2. Excipient effects on drug absorption

The influence of the pharmaceutical excipients on drug absorption was assessed through the co-administration of ampicillin and antipyrine. The individual pharmacokinetic parameters for the ampicillin and antipyrine treatments are presented in Tables 4 and 5. The corresponding mean plasma concentration time-profiles are depicted in Figs. 1 and 2.

In the absence of excipient (control treatment), the mean absolute oral bioavailability for ampicillin was 36%. The low bioavailability of ampicillin is a consequence of its poor absorption from the gastrointestinal tract, as the drug does not undergo significant pre-systemic first-pass elimination (Yano et al., 1989). Ampicillin is absorbed from the upper small intestine via a dipeptide transporter (Oh et al., 1992). The mean absolute bioavailability of antipyrine was 76%, which correlates well with similar studies conducted in beagle dogs (Vickers et al., 1989). In contrast to ampicillin, antipyrine is rapidly and completely absorbed from the intestinal tract through aqueous pores. Also noteworthy is that the T_{max} was considerably shorter for antipyrine than for ampicillin.

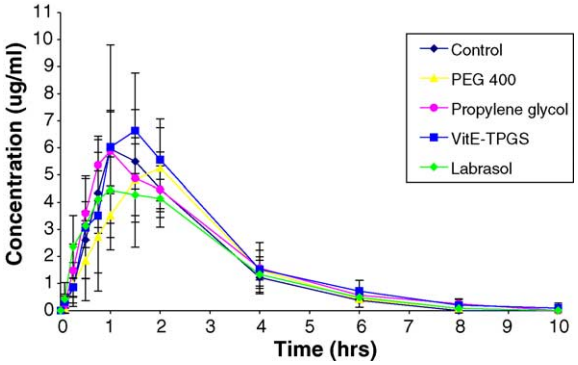

Fig. 1. Mean (±S.E.) plasma ampicillin concentration-time profiles.

In the presence of PEG 400, propylene glycol, TPGS and Labrasol, the mean absolute bioavailabilities for ampicillin were 32, 39, 42 and 32%, respectively. The corresponding mean figures for antipyrine were 74, 85, 73 and 74%, respectively. No significant difference was noted between the treatments. Moreover, there is no apparent correlation between the individual bioavailability figures and the corresponding gastrointestinal transit data, suggesting that residence time in the small intestine does not influence drug absorption. This is partly surprising in the case of ampicillin, since it is

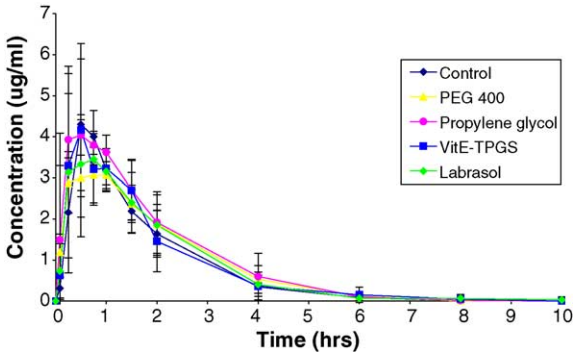

Fig. 2. Mean (±S.E.) plasma antipyrine concentration-time profiles.

Table 4
Pharmacokinetic data for ampicillin after oral administration

Treatment	Dog	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}12}$ (h μg/mL)	$AUC_{0\text{-}inf}$ (h μg/mL)	Bioavailability (%)
Control	1	6.90	1.0	15.44	16.36	31.1
	2	9.07	1.0	22.19	22.82	32.8
	3	6.48	1.0	16.67	17.62	40.6
	4	6.33	2.0	16.84	17.96	42.5
	Mean (±S.D.)	7.19 (±1.27)	1.25(±0.50)	17.79 (±3.00)	18.69 (±2.84)	36.0 (±5.65)
PEG 400	1	8.23	2.0	17.92	18.46	35.1
	2	5.23	2.0	15.15	15.65	22.5
	3	5.95	1.5	16.15	17.05	39.3
	4	5.96	2.0	15.10	16.06	38.0
	Mean (±S.D.)	6.34 (±1.30)	1.88 (±0.25)	16.08 (±1.32)	16.81 (±1.25)	32.3 (±7.68)
Propylene glycol	1	7.62	1.5	18.14	19.96	37.9
	2	7.72	1.0	21.55	22.28	32.0
	3	4.50	1.5	11.00	11.78	27.1
	4	7.97	1.5	25.48	26.23	62.1
	Mean (±S.D.)	6.95 (±1.64)	1.38 (±0.25)	19.04 (±6.14)	20.06 (±6.10)	38.6 (±15.53)
Vitamin E-TPGS	1	11.47	1.0	22.43	25.63	48.7
	2	9.70	1.5	22.62	23.62	34.0
	3	5.10	1.0	15.05	16.06	37.0
	4	6.57	2.0	19.81	23.65	56.0
	Mean (±S.D.)	8.21 (±2.90)	1.38 (±0.48)	19.98 (±3.53)	22.24 (±4.23)	42.0 (±10.27)
Labrasol	1	7.04	1.0	15.71	16.13	30.6
	2	4.98	2.0	16.65	17.77	25.6
	3	5.48	0.75	12.73	13.66	31.5
	4	5.43	2.0	18.28	19.07	45.2
	Mean (±S.D.)	5.73 (±0.90)	1.44 (±0.66)	15.84 (±2.33)	16.65 (±2.33)	32.1 (±8.40)

poorly permeable from the small intestine, and previous studies in rats have shown a link between residence time in the small intestine and the extent of absorption of this drug (Haruta et al., 1998).

PEG 400 has been shown to increase the absorption of the small hydrophilic molecule ranitidine. A combined scintigraphic and pharmacokinetic study conducted in humans revealed a significant 41% increase in ranitidine bioavailability in the presence of 1 g PEG 400 (Schulze et al., 2003). It was hypothesized that PEG 400 has an affect on the paracellular pathway; a route exploited by ranitidine to move across the epithelium. In the dog, this transport pathway is more prominent because of the increased size and frequency of the paracellular pores (He et al., 1998). In fact, the absolute bioavailability of ranitidine in dogs is 100% (Chiou et al., 2000), which is the main reason why it was not chosen as a model drug for this study. No absorption enhancing effects were observed in the present canine study for either ampicillin or antipyrine in the presence of PEG 400, possibly because of the non-paracellular absorption mechanisms used by these compounds.

The pharmacokinetics of ampicillin and antipyrine were not significantly affected by the presence of propylene glycol or TPGS. This is in line with the lack of effect on gastrointestinal transit. However, while the cosolvent propylene glycol has proven solubilizing qualities, the surfactant TPGS has additional permeation enhancing properties. TPGS inhibits the intestinal efflux transporter P-glycoprotein in Caco-2 cells (Dintaman and Silverman, 1999). Maximum efflux-inhibition was observed at surfactant concentrations below the critical micelle concentration, suggesting that TPGS monomers are responsible for the inhibition. The lack of increase in drug bioavailability in the present study is suggestive that neither ampicillin nor antipyrine is a substrate for the efflux transporter in dogs.

Table 5
Pharmacokinetic data for antipyrine after oral administration

Treatment	Dog	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}12}$ (h μg/mL)	$AUC_{0\text{-}inf}$ (hr μg/mL)	Bioavailability (%)
Control	1	4.00		5.92	6.10	64.2
	2	6.41	0.75	10.59	11.48	76.7
	3	4.71	0.25	8.27	8.39	77.4
	4	5.41	0.50	10.70	10.87	83.8
	Mean (±S.D.)	5.13 (±1.03)	0.75 0.56	8.87 (±2.26)	9.21 (±2.47)	76.3 (±8.20)
PEG 400	1	3.03	1.0	5.00	5.15	54.2
	2	6.35	0.25	12.09	12.70	84.9
	3	4.08	0.25	8.67	8.71	80.4
	4	3.28	1.0	9.01	9.22	71.1
	Mean (±S.D.)	4.19 (±1.51)	0.63 (±0.43)	8.69 (±2.90)	8.94 (±3.09)	74.1 (±13.56)
Propylene glycol	1	4.52	0.5	7.27	7.30	76.8
	2	6.55	0.25	10.79	10.96	73.3
	3	3.80	0.5	7.77	7.89	72.8
	4	5.71	0.25	14.70	14.84	114.4
	Mean (±S.D.)	5.15 (±1.22)	0.38 (±0.14)	10.13 (±3.42)	10.25 (±3.46)	84.9 (±20.14)
Vitamin E-TPGS	1	7.20	0.5	8.82	9.12	96.0
	2	5.61	0.25	8.98	9.05	60.5
	3	5.99	0.25	6.87	7.05	65.0
	4	3.95	1.0	9.68	9.79	75.5
	Mean (±S.D.)	5.69 (±1.34)	0.50 (±0.35)	8.59 (±1.20)	8.75 (±1.18)	72.5 (±15.80)
Labrasol	1	4.72	0.5	6.14	6.18	65.1
	2	4.24	1.0	11.55	11.95	79.9
	3	3.77	0.75	8.26	8.35	77.0
	4	3.77	0.75	8.94	9.06	69.9
	Mean (±S.D.)	4.13 (±0.45)	0.75 (±0.20)	8.72 (±2.23)	8.88 (±2.38)	73.6 (±6.75)

Like the aforementioned excipients, Labrasol showed a similar lack of effect on drug absorption. Medium chain glycerides have been shown to exhibit permeability-enhancing properties as a result of interactions with the phospholipid bilayer of the lining epithelium (Swenson and Curatolo, 1992). Recently, in vitro and in situ experiments described an enhanced permeation of the poorly absorbable drugs vancomycin (Prasad et al., 2003) and cephalexin (Koga et al., 2002) in preparations with Labrasol. Cephalexin is a β-lactam antibiotic, which makes use of the intestinal dipeptide transporter similar to ampicillin. In vivo studies also described absorption-enhancing effects of Labrasol for the poorly absorbable drugs gentamicin (Hu et al., 2001) and insulin (Eaimtrakarn et al., 2002) and in humans for the poorly soluble but highly permeable compound piroxicam (Yüksel et al., 2003). The lack of bioavailability enhancement in the present canine study could be possibly due to interspecies differences.

4. Conclusions

PEG 400, TPGS, propylene glycol and Labrasol do not influence gastric emptying or small intestinal transit in beagle dogs at relatively low doses of 1–2 g. Also, no significant effect on the oral bioavailability of ampicillin or antipyrine was observed in the presence of these excipients. The permeation-enhancing effect of low doses of PEG 400 previously observed in humans was not apparent in the present study possibly as a result of interspecies differences, such as the leakier absorptive membrane in canines, or because different drug candidates were used in this study. Overall, further work is necessary to fully investigate the utility of

the dog as a model for predicting the in vivo effects of pharmaceutical excipients in humans.

Acknowledgement

Julia D.R. Schulze gratefully acknowledges Glaxo-SmithKline (formerly GlaxoWellcome) for the award of a studentship.

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