

Poster Session 1 – Biopharmaceutics

027
The prediction of in-vivo drug absorption and pharmacokinetic parameters using a novel in-vitro model

L. R. Shaw, W. J. Irwin, T. J. Grattan* and B. R. Conway

Pharmaceutical Sciences Institute, Aston University, Birmingham, UK and *GlaxoSmithKline Consumer Healthcare, St George's Avenue, Weybridge, UK

Recently, the focus for the development of IVIVCs has shifted to an approach where the intestinal permeation and drug dissolution are considered jointly (Polli et al 1996). This study extends this approach by combining in-vitro dissolution and permeability methods with literature data for gastric emptying, and the use of a computer simulation of the absorption process. The model drugs selected for the study were commercial immediate release (IR) ibuprofen and paracetamol tablets. Tablet dissolution was investigated using USP apparatus II, with a paddle speed of 50 rev min^{-1}, n = 6, UV analysis, using either 400 mL of 0.05 M HCl or USP buffer pH 6.8. The dissolution profiles were approximated to a first-order relationship and the half-lives obtained. Permeability experiments were conducted using stomach and duodenum tissue sacs, obtained from Male Wistar rats (250–450 g) allowed free access to food and water, and sacrificed by cervical dislocation. Analysis was performed by HPLC or a scintigraphic method and the permeation rate constants (P_{app}) calculated. In order to model the situation in-vivo, the permeation for the paracetamol control through the intestine model was transformed to correspond with a total permeation half-life of 6.8 min (Clements et al 1978). The computer model was written in-house using Modelmaker V3.0 (Cherwell Publishing, Oxford, UK) and comprised six compartments, representing undissolved/dissolved drug in the stomach and intestine, total drug absorbed and drug eliminated. All processes were assigned as first order. For gastric emptying with a phase I pattern, a lag-time of 16 min was used, followed by an emptying half-life of 6.7 min (Macheras et al 1995). Phase III emptying of solid and liquid from the stomach were assigned half-lives of 4.9 and 2.9 min, respectively, with data obtained from literature (Oberle et al 1990).

For ibuprofen IR tablets, the dissolution rate constants were 0.069 (maximum 1% of dose) and 0.139 min^{-1} in the stomach and intestine models, respectively. The transformed permeation rate constants were 0.0102 and 0.108 min^{-1} in the stomach and intestine models, respectively. For paracetamol IR tablets, the dissolution rate was 0.139 min^{-1} in the stomach with 100% dissolution in the stomach. The permeation rate constants were 0.00679 and 0.102 min^{-1} in the stomach and intestine, respectively. The simulation predicted t_{max} values of 58 and 105 min versus average literature values of 58 min and 109 min (Shaw 2001). The % absorbed versus % dissolved profiles confirmed that the absorption of paracetamol and ibuprofen were permeability and dissolution rate-limiting, respectively.

Clements, J., et al (1978) *Clin. Pharmacol. Ther.* **24**: 420–431

Macheras, P., et al (1995) *Biopharmaceutics of orally administered drugs*. 1st edn, Ellis Horwood, London

Oberle, R., et al (1990) *Gastroenterology* **99**: 1275–1282

Polli, J. et al (1996) J. *Pharm. Sci.* **85**: 753–759

Shaw, L. (2001) PhD Thesis Aston University

L. R. Shaw would like to thank the EPSRC and Glaxo SmithKline for financial support.

028
Monolayer formation by guinea-pig gastric epithelial cells grown on polycarbonate membranes

K. M. Kavvada, J. G. Murray*, A. G. A. Coombes and P. J. Hanson

Pharmaceutical Sciences Research Institute, Aston University, Birmingham B4 7ET, UK and *AstraZeneca, Loughborough LE11 5RH, UK

The development of sophisticated tissue models for screening of novel pharmaceutical agents, dosage forms and delivery systems that interact with the gastric epithelium is assuming increasing importance. The mucous cells, which make up the surface of the gastric epithelium, constitute a major component of the gastric barrier and exhibit major differences from the cell-types which line the small intestine. The overall aim is to develop a preparation of guinea-pig gastric epithelial cells grown on porous polycarbonate support membranes for use in biopharmaceutical screening. A key feature of any model is that the cells form a monolayer with tight junctions. This presentation considers how attachment factors, the pore size of the support and the composition of the culture medium affect monolayer formation.

Cells were isolated as described by Ashton & Hanson (2002), and were plated on polycarbonate transwells with a surface area of 4.7 cm^2. Cells were cultured in RPMI 1640 medium plus 10% fetal calf serum, 100 U mL^{-1} penicillin, 100 μg mL^{-1} streptomycin, 2.5 μg mL^{-1} amphotericin B and 10 ng mL^{-1} of epidermal growth factor for 72 h before assay. Measurements of permeability were performed with culture medium replaced by Hank's balanced salt solution. Gastric mucosal fibroblasts, which may release molecules which affect epithelial cell growth and function, were prepared by maintaining a gastric mucosal cell isolate in culture for 26 days. Transwells were coated with type I collagen by incubation with a 0.1 mg mL^{-1} solution for 6 h at 37°C. Transwells were subsequently dried overnight under UV illumination. Monolayer formation was evaluated from the rate of fluorescein transfer (paracellular permeability), trans-epithelial resistance (TER) and visual inspection of cell monolayers after fixation and staining with crystal violet.

Coating of transwells with type I collagen effected an 88% reduction in the apparent permeability of fluorescein ($P < 0.001$) compared with uncoated supports. Permeability of fluorescein was 76% lower when the pore size of the collagen-coated polycarbonate membrane was 0.4 μm rather than 3 μm ($P < 0.001$). Increasing the Ca^{2+} concentration in the culture medium from 0.4 to 2 mM, 24–72 h before assay, prevented monolayer formation on collagen I-coated, 0.4-μm-pore transwells. Using the same design, replacement of half the culture medium with conditioned medium taken from a primary culture of gastric mucosal fibroblasts had no effect on subsequent fluorescein permeability or TER. On collagen-I-coated, 0.4-μm-pore transwells, TER was 679 ± 50 ohms cm^2 (3 separate cultures), which is similar to the TER of intact sheets of guinea-pig gastric mucosa in vitro (Yanaka et al 1996).

In conclusion, when guinea-pig gastric mucous cells were grown on a 0.4-μm polycarbonate membrane coated with collagen type I a monolayer was formed, the TER of which was similar to that of intact sheets of guinea-pig gastric mucosa.

Ashton, M., Hanson, P. J. (2002) *Br. J. Pharmacol.* **135**: 407–416

Yanaka, A., et al (1996) *Am. J. Physiol.* **271**: G75–G85

029
Preparation and evaluation of mucoadhesive microspheres containing triclosan for delivery to the oral cavity

Sandra Kockisch, Gareth D. Rees*, Simon A. Young, John Tsibouklis and John D. Smart

Biomaterials and Drug Delivery Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, White Swan Road, Portsmouth PO1 2DT, UK and *GlaxoSmithKline, St George's Avenue, Weybridge, Surrey, KT13 0DE, UK

The efficacy of conventional formulations for local drug delivery to the oral cavity is limited by the rapid clearance of active components following administration, due to salivation and the subsequent swallowing reflex. The aim of this work was to develop a novel paste formulation based on drug-loaded mucoadhesive microparticles and to then investigate their potential advantage for the controlled release of an antimicrobial agent in the oral cavity.

Microspheres were prepared from the polymers Carbopol 974P NF, polycarbophil Noveon AA-1, chitosan (low molecular weight) and Gantrez MS-255, using a water-in-oil (W/O) emulsion solvent evaporation method. Triclosan, an anti-

microbial commonly used in oral healthcare, is sparingly soluble in water, so was incorporated into the polymer particles by an especially developed double emulsion (O/W/O) solvent evaporation technique.

Mean particle sizes were determined by laser light diffraction to be typically in the range 23–38 μm. Scanning electron microscopy characterisation revealed that both the drug-free and drug-loaded microparticles were smooth and spherical in all cases. Examination of individual cryosectioned triclosan-containing microparticles demonstrated that the particles were effectively homogeneous matrix microspheres rather than microcapsules. The microparticles exhibited significantly increased swelling ratios in pH 7.0 phosphate buffered saline and longer half-times of swelling in PBS relative to the original powdered polymer.

The in-vitro mucoadhesive behaviour, evaluated by means of tensile and duration of adhesion tests modified from that described by Mortazavi & Smart (1994, 1995), was compared with a negative control (30-μm tristearin microparticles). In all cases (Table 1) the maximum force of detachment (F_{max}), the total work of adhesion (W_{ad}) and the duration of adhesion (t_{ad}) were statistically greater for the polymers than for the control.

Table 1 Summarised results for the tensile (n = 15) and duration of adhesion tests (n = 10)

	F_{max} (mN)	W_{ad} (μJ)	t_{ad} (h)
Tristearin	2.8 ± 1.7	1.01 ± 0.6	0.0 ± 0.0
Carbopol	50.0 ± 19.4	57.0 ± 26.0	4.45 ± 1.39
Polycarb.	55.1 ± 20.2	56.6 ± 22.2	4.39 ± 1.87
Chitosan	40.6 ± 11.9	42.3 ± 18.2	0.61 ± 0.24
Gantrez	44.1 ± 14.8	36.5 ± 15.9	3.31 ± 0.99

Data are means ± s.d.

Drug-loaded microparticles were found to contain triclosan at levels in the range 3.2–7.5% (w/w) by extracting the drug and evaluating by UV spectroscopy. The loading was dependent on the initial ratio of polymer to drug, but also on the nature of the polymer itself. Entrapment of triclosan by Carbopol and polycarbophil microparticles appeared to be less efficient than was the case with chitosan or Gantrez.

It was concluded that triclosan-loaded bioadhesive particles could be formulated. To complete the present phase of this study, the kinetics of triclosan release from the polymer microparticles in artificial saliva is currently under investigation, along with the particles retention on mucosal surfaces in simulated in-vivo conditions.

Mortazavi, S. A., Smart, J. D. (1994) *J. Contr. Release* **31**: 207–212
Mortazavi, S. A., Smart, J. D. (1995) *Int. J. Pharmaceutics* **116**: 223–230

030
Investigation of Azone-induced fluidity in lipid membranes using a thickness shear mode sensor

M. Reason, R. Latham*, B. Henry† and G. Smith

School of Pharmacy, *Department of Chemistry, De Montfort University, Leicester, LE1 9BH UK and †Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK

Azone has been used to improve drug flux across skin and is thought to work by increasing the fluidity of the intercellular lipid of the stratum corneum. Conventional techniques investigating membrane fluidity either require the incorporation of a marker into the lipid membrane, or are limited to the investigation of a specific region of the membrane (e.g. the vibrational modes of the hydrocarbon chains). In contrast, the thickness shear mode (TSM) sensor is an acoustic device that can measure both changes in the mass and fluidity, at the mesoscopic scale, of a lipid matrix (such as the stratum corneum).

Impedance analysis of 8 MHz TSM sensors coated with a lipid matrix developed by Moghimi et al (1996), but with increasing concentrations of Azone included, was performed using a Hewlett Packard E5100A network analyser. The lipid matrix was coated on to the sensor using a spin coating technique and then hydrated in water at 60°C. Frequency shifts of the lipid matrix coated sensor were determined from the impedance spectra and interpreted in terms of mass loading, using the relationship proposed by Sauerbrey (1959). Changes in the fluidity of the matrix were interpreted from changes in the shape of the biosensor impedance spectra and quantified using the magnitude of the impedance minimum (Table 1).

Table 1 Change in impedance minimum with increasing mole % of Azone in the lipid matrix

Mole % Azone	Normalised average impedance minimum/Ω
0	1.00 ± 0.67
5	1.22 ± 0.69
10	1.85 ± 0.69
15	2.01 ± 0.96
20	2.83 ± 0.72

Data is normalised against the frequency shift due to the Deposition of lipid on the sensor and the impedance minimum of the 0% Azone film

Table 1 shows that the normalised impedance minimum of the lipid matrix coated sensor increases with increasing mole % of Azone, indicating that the fluidity of the lipid matrix increases with the amount of Azone in the film. This change in fluidity is probably due to a decrease in lipid order or an increased hydration of the lipid matrix. These mesoscopic changes in membrane fluidity are consistent with the microscopic observations of Harrison et al (1996), who used FT-IR to measure a decrease in order and an increase in the motion of the hydrocarbon chains of the stratum corneum lipids on treatment with deuterated Azone.

Harrison, J. E., et al (1996) *J. Control. Release* **41**: 283–290
Moghimi, H. R., et al (1996) *Int. J. Pharmaceutics* **131**: 103–115
Sauerbrey, G. W. (1959). *Zeitschrift fur Physik*. **155**: 206–212

Project supported by Pfizer central research and De Montfort University.

031
Reduction in bioavailability of rifampicin in presence of isoniazid from fixed dose combination (FDC) formulation envisaged from plasma level study

S. S. Savale, K. A. Prajapati, I. S. Rathod, S. A. Shah and C. J. Shishoo

Dept. of Quality Assurance, L. M. College of Pharmacy, Navrangpura, Ahmedabad, India

Degradation of rifampicin (RIF) to inactive 3-formyl rifamycin SV (3-FRSV) is enhanced by isoniazid (INH), in acidic conditions prevailing in stomach (Shishoo et al 1999; Singh et al 2000). Implication of this fact has been reflected in the impairment of RIF bioavailability when RIF is administered as a Fixed Dose Combination (FDC) capsule with INH as compared with a single component RIF capsule, based on the urinary excretion data (Shishoo et al 2001). It was observed that bioavailability of RIF decreased by about 32% when administered as FDC capsule.

To receive direct confirmation of the incompatability of RIF and INH in terms of bioavailability of RIF, a comparative bioavailability study, based on plasma levels of RIF and its major metabolite 25-desacetyl rifampicin (25-DAR), was carried out. The bioavailability of RIF after administration of RIF-INH FDC capsule (450 mg + 300 mg) was compared with that of RIF capsule (450 mg) by conducting a single-dose, two-treatment, two-period, cross-over study in five healthy subjects. Plasma levels of RIF and 25-DAR were monitored using a specific HPTLC method. Using plasma concentration–time data after each treatment, various pharmacokinetic parameters for both RIF and 25-DAR, were calculated (Table 1). Significant reduction in the bioavailability (~24% as RIF and ~17% as 25-DAR) of RIF, from FDC capsule as compared with RIF capsule was observed.

Table 1 Pharmacokinetic parameters of RIF and 25-DAR after administration of RIF capsules and RIF-INH FDC capsules

Parameter	RIF capsule[a]		(RIF-INH) FDC capsule[a]		% decrease[b]	
	RIF	25-DAR	RIF	25-DAR	RIF	25-DAR
C_{max} ($\mu g\,mL^{-1}$)	14.35 ± 1.16	4.14 ± 1.28	11.64 ± 1.29	3.38 ± 1.05	18.89	18.36
T_{max} (h)	2.55 ± 1.04	5.60 ± 0.89	1.90 ± 0.45	5.60 ± 1.67	—	—
$AUC_{0\text{-}12}$ ($\mu g\,h\,mL^{-1}$)	82.31 ± 9.69	29.49 ± 8.88	62.33 ± 4.48	24.61 ± 9.13	24.27	16.55
$AUC_{0\text{-}\infty}$ ($\mu g\,h\,mL^{-1}$)	94.02 ± 10.94	41.61 ± 16.80	74.67 ± 14.64	38.67 ± 11.21	—	—
k_{el} ($L\,h^{-1}$)	0.215 ± 0.039	0.159 ± 0.037	0.220 ± 0.081	0.127 ± 0.026	—	—
$t_{1/2el}$ (h)	3.32 ± 0.66	4.57 ± 1.06	3.62 ± 1.67	5.67 ± 1.33	—	—

[a]All the values indicate mean ± s. d. (n = 5).
[b] % decrease in bioavailability parameter after administration of RIF-INH FDC capsule as compared with RIF capsule

Statistical comparison of the bioavailability parameters (two one-sided t test and 90% confidence interval for ratio) indicated reduction in bioavailability of RIF from FDC with respect to single component RIF formulation.

It, thus, underlines the fact that there is an urgent need to develop alternative, stable combination formulation in order to minimize RIF degradation in the gastrointestinal tract and assure optimum bioavailability of RIF.

One of the authors (S.S.S.) is thankful to CSIR, New Delhi, for financial assistance.

Shishoo, C. J., et al (1999) *Int. J. Pharmaceutics* **190**: 109–123
Shishoo, C. J., et al (2001) *Int. J. Pharmaceutics* **228**: 53–67
Singh, S., et al (2000) *Pharm. Pharmacol. Commun.* **6**: 491–494

032

The mucosal retention of ^{14}C- labelled poly(acrylic acids) on gastric and oesophageal mucosa: an in-vitro study

Robert G. Riley, John D. Smart, John Tsibouklis, Simon A. Young, Frank Hampson,* Alf Davis,* Grant Kelly,* Peter W. Dettmar* and William R. Wilber**

Biomaterials and Drug Delivery Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, St Michael's Building, White Swan Road, Portsmouth PO1 2DT, UK, *Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK and **Noveon Inc., 9911 Brecksville Road, Brecksville, OH 44141-3247, USA

Polymers that bind from solution on to gastric mucosa can be used either as a means of facilitating localised drug delivery, or can act as therapeutic agents in their own right (e.g. by forming a protective layer or by inhibiting enzymes). In our previous study (Riley at al 2002), the binding and retention of labelled poly(acrylic acid)s with differing physicochemical properties on sections of gastric mucosa from pigs was evaluated using a dynamic flow study (Young & Smart 2000). In this model, polymer solutions were applied to a section of frozen and thawed mucosa (15 mm × 120 mm), inclined at 30° and washed with simulated gastric acid (0.01 M HCl, 1 mL min^{-1}, 37°C). In the current study, solutions (0.5 g, 3%, pH 4.3) of low-molecular-weight (average MW 140 000), high-molecular-weight (average MW 2 960 000) and ultra-high-molecular-weight (MW 10^6–10^9) ^{14}C containing poly(acrylic acid)s (Riley et al 2001) were evaluated in the dynamic flow model for their ability to bind to tissues from the fundic and pyloric regions of the stomach and the oesophagus of pigs.

All the polymers were found to bind to, and be retained on, each mucosa for extended periods (Table 1); the high- and ultra-high-molecular-weight polymers showed the greatest retention characteristics after 20 min. Examination of the kinetics of polymer elution suggested that, after an initial lag phase (T_{lag}), two fractions appear to exist, bound and unbound polymer, showing differing retention profiles. The unbound polymer was washed off relatively rapidly while the bound polymer was retained for over 20 min (Table 1). The high-molecular-weight polymer gave the greatest retention on pyloric tissue, while the ultra-high- and high-molecular weight polymer showed similar retention on both the fundic and oesophageal mucosa.

Table 1 Modelled and actual retention of polymers after 20 min (n = 3–4)

Polymer	T_{lag} (min)	Half-life (min) unbound polymer	% Retention at 20 min Modelled	Actual (s.d.)
Oesophagus tissue				
Low	−0.07	0.37	22.42	22.5 (2.2)
High	1.29	3.88	37.63	38.4 (3.9)
Ultra high	0.67	2.90	31.04	31.4 (1.6)
Fundus tissue				
Low	−0.19	0.11	2.96	2.9 (4.0)
High	0.55	2.57	38.33	38.5 (1.3)
Ultra high	0.69	1.81	21.99	22.2 (2.4)
Pyloric tissue				
Low	−0.23	0.21	13.67	13.7 (0.3)
High	1.81	69.88	63.21	63.5 (1.9)
Ultra high	0.28	1.27	24.14	25.4 (0.1)

A clear relationship between the nature of the mucosae (e.g. stratified or columnar) and retention was not obvious. It was concluded that the poly(acrylic acid) retention on these mucosae presents a therapeutic opportunity. The differences in binding and retention of the polymers on the different mucosae could present the possibility of targeting within the gastrointestinal tract.

Riley, R. G., et al (2001) *J. Biomed. Mat. Res.* (*Appl. Biomat.*) **58**: 102–107
Riley, G., et al (2002) *Int. J. Pharmaceutics* **236:** 87–96
Young, S. A., Smart, J. D. (2000) *J. Pharm. Pharmacol.* **52** (Suppl.): 167

033

Bioadhesion from solution — an in-vitro study of the binding of labelled chitosan

D. Patel and J. D. Smart

Biomaterials and Drug Delivery Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth UK PO1 2DT, UK

A macromolecular carrier that will bind to the mucosal surfaces of the oral cavity, and be retained for extended periods, provides the opportunity for extended drug delivery. In previous work, chitosan was identified as being able to adsorb onto oral epithelial cells in-vitro (Patel et al 1999) and be retained in-vivo for over an hour (Kockisch et al 2001). In this study, chitosan will be radiolabelled to allow the quantification of binding to isolated buccal cells and a model mucous membrane. Chitosan (SeaCure 240) was partially reacetylated by mixing 0.3 g with 0.93 mL ^3H acetic anhydride in a methanol, pyridine, acetic acid solvent for 5 h, then dialysing against distilled water for 24 h and freeze drying. The degree of reacetylation was determined by NMR as being 31.7% of available amine groups. Using the technique of Patel et al (1999), buccal cells scraped from the inner cheek of human subjects were washed and made to a standard concentration per test, and then exposed to solutions of chitosan (2 mL, 0.5%, pH 4.5) in distilled water, for 15 min at 30°C. The cells were then washed 5 times with isotonic tris buffered saline (pH 7.6), then dissolved in 0.1 M NaOH, and the activity determined. In a second study, circular sections of porcine oesophageal tissue (4.91 cm^2) were carefully washed, exposed to the polymer solution (2 mL) for 15 min at 30°C in the static apparatus described by Riley et al (2002). The oesophageal sections were washed 5 times with buffered saline, and the tissue dissolved in 0.1 M NaOH before scintillation counting. Both experiments were completed five times.

For the buccal cells, 2.43% (s.d. 0.43) of the applied chitosan was found to adsorb onto 48 × 10^4 buccal cells, which is equivalent to 515.85 ρg (s.d. 89.6) per cell. For the oesophageal mucosae, 3.48% (s.d. 0.04) was absorbed onto each section, giving 732.2 ρg (8.98) per cm^2. A tentative extrapolation from these figures

predicts that 3–12 mg of chitosan would bind to a typical human oral cavity. However, the partial reacetylation of chitosan was observed to reduce binding when assessed using the lectin-inhibition technique of Patel et al (1999), so binding of the non-reacetylated molecule would be expected to be much higher. However, the effect on binding of the presence of saliva and foodstuffs will need to be considered in further studies.

Kockisch, S., Rees, G. D., Young, S. A., et al (2001). *J. Control. Release* **77**: 1–6
Patel, D., Smith, A. W., Grist, N. W., Barnett, P., Smart, J. D. (1999) *J. Control. Release* **61**: 175–183
Riley, R. G, Smart, J. D., Tsibouklis, J. T., et al (2002) *Int. J. Pharm*aceutics **236**: 87–96

034
Disintegration of tablets in complex media

Sadaf Anwar, John T. Fell, and Paul Dickinson*

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK and *Astra Zeneca, Alderley Park, Macclesfield, SK10 4TG, UK

The advent of the Biopharmaceutical Classification System has led to the reassessment of compendial test media to provide good predictability of the in-vivo performance of a dosage form (Amidon et al 1995). It is well known that in-vitro test conditions in use at present do not simulate the physiological environment of the gastrointestinal tract with respect to fluid composition or intensity of agitation. Thus, compliance with compendial tests does not guarantee in-vivo efficacy, due to the lack of similarity between in-vitro and in-vivo conditions, and as such, there is an inability to predict in-vivo performance from in-vitro data (Horter & Dressman 1997).

Thus, in recent years, interest has focused on the development of physiologically relevant media which attempt to mimic the in-vivo conditions of the gastrointestinal tract, due to the need for more predictive in-vitro test methods. As a result, several media have been suggested to be physiologically relevant, which has resulted in improved in-vitro/in-vivo correlations compared with the standard tests employed at present (Dressman et al 1998; Galia et al 1998). Although dissolution has been examined in detail, little work has been carried out on assessing the preliminary step in dissolution, namely, disintegration. Alterations in media composition that would affect factors such as surface tension and viscosity would be expected to influence tablet disintegration and it is the aim of this study to examine the disintegration of tablets in physiologically relevant media.

The standard BP 2000 test with discs was used to assess disintegration times. Each test was carried out in triplicate using six tablets for each test. Two sets of tablets were prepared, representing rapidly disintegrating systems (25 s in water, microcrystalline cellulose, 65%; lactose 31%; magnesium stearate 3%; Explotab, 1%) and poorly disintegrating systems (8 min in water, microcrystalline cellulose 95%: magnesium stearate, 5%). Tablets were prepared individually on a hydraulic press. Ten media were chosen from the literature to represent conditions in the stomach where conventional tablets would be expected to disintegrate. For the rapidly disintegrating tablets, little difference was found in disintegration times when the different media were employed. For the poorly disintegrating tablets, significant increases in disintegration times, up to three times that in water, were observed when employing media such as whole milk and simulated gastric fluid USP 23 with and without pepsin.

The initial step in disintegration is penetration of fluid into the tablet and differences in the surface tensions and viscosities of the media together with the potential for interactions may influence penetration and explain these results.

Amidon, G. L., Lennernas, H., Shah, V. P., et al (1995) *Pharm. Res.* **12**: 413–420
Dressman, J. B., Amidon, G. L., Reppas, C., et al (1998) *Pharm Res* **15**: 11–22
Galia, E., Nicolaides, E., Horter, D., et al (1998) *Pharm. Res.* **15**: 698–705
Horter, D., Dressman, J. B. (1997) *Adv. Drug Deliv. Rev.* **25**: 3–14

035
The effect of different concentrations of polyethylene glycol 400 on gastrointestinal transit

J. D. R. Schulze, W. A. Waddington*, P. J. Ell*, M. D. Coffin**, G. E. Parsons† and A. W. Basit

Department of Pharmaceutics, School of Pharmacy, University of London, UK, *Institute of Nuclear Medicine, Middlesex Hospital, University College London, UK, **Glaxo-SmithKline, Research Triangle Park, NC, USA and †GlaxoSmithKline, Ware, UK

Solubility in the gastrointestinal fluid is a major factor limiting the oral bioavailability of many drugs. The solubility of such drugs can be improved by the addition of cosolvents such as polyethylene glycol 400 (PEG 400) into the formulation. Recently, however, our group have shown that PEG 400, at a dose of 10 g, accelerates the passage of oral liquids through the gastrointestinal tract, reducing the mean small intestinal transit time (MSITT) by 35% (Basit et al 2001). Since most drug compounds are primarily absorbed from the small intestine, a decrease in the MSITT is expected to have a detrimental effect on drug bioavailability. The aim of this study was to investigate whether an accelerating effect on small intestinal transit is also seen with lower doses of PEG 400.

Seven male subjects (six healthy and one type-1 diabetic) participated in an open four-way crossover study, which had been approved by the Joint UCL/UCLH Committees on the Ethics of Human Research. Each subject received, on separate occasions, 150 mL water containing 0 (control), 1, 2.5 or 5 g PEG400. The solutions were radiolabelled with technetium-99m to allow their transit to be followed using a dual-headed gamma camera.

The gastrointestinal transit (gastric emptying, small intestinal transit and caecum arrival) results are presented in Table 1. The emptying of the solutions from the stomach was rapid and no significant difference was observed between the treatments. In contrast, the transit of the various formulations through the small intestine appeared to follow a remarkable trend, as the presence of increasing amounts of PEG400 resulted in decreasing transit times. The reduction in the MSITT in the presence of 1, 2.5 and 5 g PEG 400 compared with the control was 12, 20 and 30%, respectively.

Table 1 Effect of different concentrations of PEG400 on gastrointestinal transit (mean ± s.d.)

	Control	1 g PEG	2.5 g PEG	5 g PEG
MGRT	12 ± 4	11 ± 3	22 ± 26	12 ± 3
P value[a]		0.416	0.417	0.820
MSITT	326 ± 117	286 ± 66	259 ± 71	227 ± 54
P value[a]		0.220	0.015	0.036
MCAT	339 ± 119	297 ± 67	281 ± 72	239 ± 54
P value[a]		0.216	0.059	0.036

MGRT = mean gastric residence time (min); MSITT = mean small intestinal transit time (min); MCAT = mean caecum arrival time (min). [a]Paired Student's *t*-test

It is concluded that PEG 400 accelerates small intestinal transit in a concentration dependent manner, giving an effect even at concentrations as low as 1g PEG 400. This is expected to have major implications for the use of PEG 400 in the formulation of oral solutions and soft gelatin capsules.

Basit, A. W., et al (2001) *Pharm. Res.* **18**: 1146–1150