ELSEVIER

International Journal of Pharmaceutics 236 (2002) 27–34

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

# Evaluation of Pulsincap™ to provide regional delivery of dofetilide to the human GI tract

Howard N.E. Stevens [a,*], Clive G. Wilson [a], Peter G. Welling [a], Massoud Bakhshaee [b], Julie S. Binns [b], Alan C. Perkins [c], Malcolm Frier [c], Elaine P. Blackshaw [c], Margaret W. Frame [d], Don J. Nichols [d], Michael J. Humphrey [d], Steve R. Wicks [d]

[a] *Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK*
[b] *Scherer DDS Ltd, Clydebank, UK*
[c] *Department of Medical Physics, Queen's Medical Centre, Nottingham, UK*
[d] *Pfizer Central Research, Sandwich, UK*

Received 8 January 2001; received in revised form 17 December 2001; accepted 10 January 2002

**Abstract**

Pulsincap™ formulations designed to deliver a dose of drug following a 5-h delay were prepared to evaluate the capability of the formulation to deliver dofetilide to the lower gastrointestinal (GI) tract. By the expected 5-h release time, the preparations were well dispersed throughout the GI tract, from stomach to colon. Plasma analysis permitted drug absorption to be determined as a function of GI tract site of release. Dofetilide is a well-absorbed drug, but showed a reduction in observed bioavailability when delivered from the Pulsincap™ formulations, particularly at more distal GI tract sites. Dispersion of the drug from the soluble excipient used in this prototype formulation relies on a passive diffusion mechanism and the relevance of this factor to the reduced extent and consistency of absorption from the colon is discussed. In these studies the effects of the degree of dispersion versus the site of dispersion could not be ascertained; nevertheless the scintigraphic analysis demonstrated good in vitro–in vivo correlation for time of release from Pulsincap™ preparations. The combination of scintigraphic and pharmacokinetic analysis permits identification of the site of drug release from the dosage form and pharmacokinetic parameters to be studied in man in a non-invasive manner. 

*Keywords:* Pulsatile release; Site-release; Gamma scintigraphy; Pharmacokinetics; Dofetilide; Pulsincap™

## 1. Introduction

For most immediate release drug formulations, absorption is complete by the time the swallowed dose has reached the colon and the extent of absorption in the distal gut is of little consequence. The situation is markedly different when

* Corresponding author. Tel.: +44-141-548-2441; fax: +44-141-552-6443.
*E-mail address:* h.n.e.stevens@strath.ac.uk (H.N.E. Stevens).

0378-5173/02/$ - see front matter 
PII: S0378-5173(02)00012-1

oral sustained or delayed release formulations are employed, where the extent of absorption is more susceptible to regional differences in drug absorption and gut transit times. Using scintigraphic techniques, many studies have demonstrated quantitative differences in the extent and rate of absorption as the formulation arrives in the distal small intestine and proximal colon (Wilson et al., 1991; Olsson et al., 1995).

It follows from these observations that a prerequisite for the development of sustained release dosage form for a specific drug, is a knowledge of the extent of absorption of that drug throughout the length of the gastrointestinal (GI) tract. In the past, various experimental methods have been employed to investigate drug absorption in man which have often involved invasive intubation techniques (Barr et al., 1994; Chan et al., 1994; Vidon et al., 1989) or complex formulation assemblies (Gardner et al., 1997).

It has been appreciated for a long time that the intubation process itself can disturb the normal physiological function of the GI tract and cause any resulting drug absorption data to be questioned (Read et al., 1983). The formulation approaches employed to date can be loosely categorised as being either engineering-based or adaptations of classical formulation technology. The engineering-based systems, which generally rely on an external stimulus to trigger release from the device, include the HF capsule (Antonin, 1993), the telemetric capsule (Lambert et al., 1991) and the Intellisite® capsule (Gardner et al., 1997; Parr et al., 1999).

The HF capsule has been widely used to study drug absorption (Fuhr et al., 1994; Harder et al., 1990; Staib et al., 1989) but suffers from the disadvantages that it is only suitable for liquid drug formulations and requires the use of X-ray to follow GI transit. The Lambert telemetric capsule appears to be too complex to have gained acceptance, however Intellisite® has been widely employed and has the advantage that it can be tracked through the GI tract using non-invasive gamma scintigraphy. It is reported to be suitable for carrying both liquid and solid formulations, although its consistency in releasing solid drug formulations in the low-fluid environment of the distal GI tract has been questioned (personal communication, M.J. Humphrey) and Intellisite is now being superseded by an improved design, the Enterion Capsule (Connor et al., 2001).

The most commonly employed formulation systems rely on time-dependent mechanisms to provoke drug release from capsule devices using gamma scintigraphic techniques to visualise the site of release. An early prototype capsule device comprised a water permeable hydrogel capsule in which the internal cavity contained a mixture of drug with an expanding material; the contents being sealed inside the capsule by a hydrogel plug (Rashid, 1990). Water diffused through the hydrogel wall inducing swelling of the contents and expulsion of the plug, causing drug to be released predictably in the colon after a 5-h mouth to colon transit period (Wilding et al., 1992).

The Pulsincap™ device (McNeil et al., 1994) (P-CAP) comprises an impermeable capsule body containing a drug formulation sealed in the capsule with a hydrogel polymer plug. The plug expands in water or GI tract fluid and slowly exits the capsule body, releasing the capsule contents after a defined time-delay determined by the length of the hydrogel plug (Binns et al., 1993). It has been employed in human studies for colon targeting (Bakhshaee et al., 1992; Binns et al., 1996; Wilson et al., 1997; Hebden et al., 1999a,b) in timed-release modes as well as gastroresistant configurations. An alternative version of P-CAP, in which the hydrogel plug is replaced by an eroding tablet, has been described (Stevens et al., 1995; Krögel and Bodmeier, 1998; Ross et al., 2000).

In contrast to the inherent variability associated with the gastric emptying of single unit dosage forms, transit through the small intestine is reproducible at about 3–4 h (Wilson and Washington, 1988). With a dosage form releasing purely on a time-basis, it would be expected to be variably distributed within the GI tract, and thereby permit assessment of regional absorption from a range of sites. In this study we have used a 5-h delay P-CAP to deliver dofetilide to different sites in the GI tract, employing scintigraphy and pharmacokinetic analysis to evaluate its performance in providing regional drug delivery. Dofetilide was used as the experimental drug, being a weak

base ($pK_a$ 7.0) with moderate lipophilicity (log $D$ 0.96 at pH 7.4) and exhibiting linear pharmacokinetics and complete bioavailability after conventional oral administration (Smith et al., 1992). Dofetilide is a potent cardiovascular drug and its regional absorption had not previously been explored and was of interest in the context of future formulation strategies. Three doses were investigated in the study in order to investigate whether the kinetics of absorption from distal sites were linearly related to dose.

## 2. Materials and methods

### 2.1. Preparation of radiolabelled Pulsincap™ dosage forms

All P-CAP components were supplied by Scherer DDS Ltd and consisted of size 0 gelatin capsule bodies coated with ethylcellulose (95%) and diethylphthalate (5%). The hydrogel polymer plug was prepared as rods by cross-linking polyethylene glycol (PEG molecular weight 8000) using 1,2,6-hexanetriol and dicyclohexylmethane-4,4-diisocyanate. The cross-linking reaction was catalysed by ferric chloride and the polymer washed in butylated hydroxyanisole solution (0.025%) before being cut into plugs of appropriate dimensions to afford a 4–5 h in vitro release time. The devices were assembled in the Department of Medical Physics, QMC, Nottingham using the configuration in Fig. 1. Capsules contained lightly compacted powdered sucrose as excipient. A solution of $^{111}$In-DTPA (0.5 MBq) was added to a small quantity of sucrose, dried, and added to the surface of the sucrose in the capsule. Dofetilide was supplied by Pfizer Central Research, and weighed (0.25, 0.5 and 1.0 mg) onto the surface of the labelled sucrose in the open capsule and gently mixed.

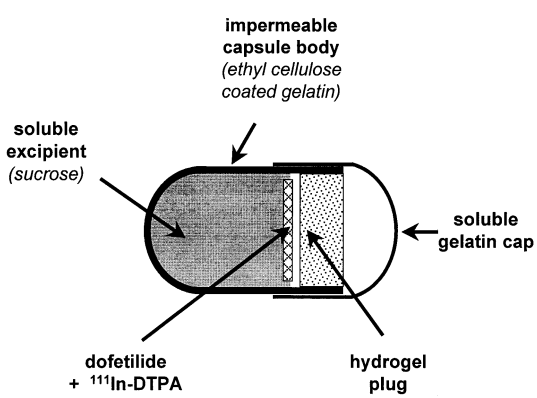


Fig. 1. Configuration of Pulsincap™ used in the study.

### 2.2. Study design

An open, four-way crossover study in which male fasted subjects were dosed on four occasions with an interval of 7 days between dosing. In addition to the three doses of dofetilide administered from P-CAP, each subject also received dofetilide (1 mg) as a solution. Eleven subjects entered the study. The study conformed to the Declaration of Helsinki and the protocol was reviewed and approved by the local ethics committee at the University of Nottingham Medical School. ARSAC approval was obtained prior to initiation of the study.

### 2.3. Study protocol

On the study day, volunteers arrived in the Department of Medical Physics, QMC, having fasted from 21:00 h the previous evening. Anterior and posterior markers containing a small amount of $^{111}$In label were taped to the abdomen of each volunteer, above the hepatic flexure, to allow accurate alignment of sequential images. Between 7.30 and 9.00 a.m., each volunteer ingested either a P-CAP with 240 ml water or a solution of 1 mg dofetilide dissolved in the same volume of water. Using a single headed gamma camera fitted with a medium energy collimator, serial anterior and posterior static scintigraphic images of 30 s duration were taken immediately following administration and at 15 min intervals around the expected time of drug release as well as at longer intervals throughout the day. The subjects remained fasted until the first meal at 4 h post dosing, followed by a second standard meal at dose + 11 h.

Following each imaging interval a blood sample (5 ml) was taken from a forearm vein, plasma was

separated, and dofetilide concentrations in plasma were determined by validated radioimmunoassay (Walker et al., 1991). The analytical method was chosen for unchanged dofetilide and response was linearly related to dofetilide concentrations in plasma with a lower limit of detection of 50 pg/ml, with inter-assay variability ranging from 5–18% over the assay range.

### 2.4. Data analysis

From the scintigraphic analysis, the time of gastric emptying, arrival at the ileocaecal junction and entry into the colon were recorded. The time of capsule opening, as determined by spreading of radiolabel in the GI tract contents, was determined by examination of the scintiscans. Pharmacokinetic parameter values ($C_{max}$, $T_{max}$, $AUC_{(0-48}$ h)) and elimination $T_{1/2}$ from the solution dose of dofetilide were determined by fitting individual plasma data sets to the pharmacokinetic one-compartmental model with first order drug input and output using software WinNonlin Version 3. Following the P-CAP 0.25, 0.5 and 1.0 mg doses, plasma dofetilide profiles did not lend themselves to pharmacokinetic modelling and pharmacokinetic parameter values were determined directly from observed data.

## 3. Results and discussion

### 3.1. In vivo study

Eight subjects completed the study receiving all four treatments. One subject received the 1.0 mg solution dose only, and one subject the solution and 0.25 mg P-CAP doses only. One subject received just the 0.25 and 0.5 mg P-CAP doses.

GI transit rate data are summarised in Fig. 2. Gastric emptying of the P-CAP formulations was generally rapid, although one capsule remained in the stomach for the duration of the study. Small intestinal transit, arrival at the ileocaecal junction, and entry into the colon compared favourably with literature values for non-disintegrating formulations. Site of release of drug and scintigraphic marker into the GI tract varied, with one

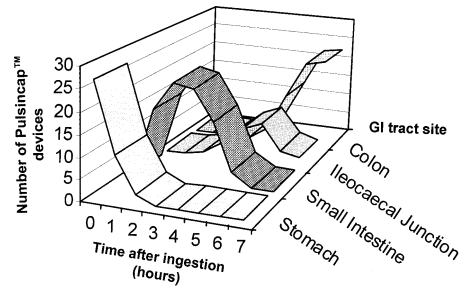


Fig. 2. GI transit of Pulsincap™ in fasted volunteers ($n = 27$).

capsule being retained in the stomach and the others being distributed along different regions of the GI tract (small intestine (9), ileocaecal junction (7) and colon (10)).

### 3.2. Pharmacokinetic analysis

Results of pharmacokinetic analysis of the dofetilide solution data are given in Table 1 and the data for the P-CAP doses is shown in Table 2 as a function of dofetilide dose and site of release.

An excellent fit was obtained by the ascribed one compartment open model with first order absorption and elimination to individual plasma data sets following the solution 1.0 mg dose. The mean correlation coefficient of goodness of fit of observed data to model values was 0.97. Following the solution dose, a mean peak dofetilide concentration of 6.4 ng/ml was obtained at 1.7 h. There was no absorption lag-time. Elimination of dofetilide from plasma, after peak plasma levels have been reached, occurred with a half-life of 6 h. The mean $AUC_{(0-48\ h)}$ was 75 ng h/ml.

Plasma concentrations following P-CAP doses were consistently lower than from the 1 mg solution dose. The expected lag-time of approximately 5 h occurred before dofetilide could be detected at a measurable concentration in plasma. Subsequent absorption of dofetilide was generally prolonged with mean $T_{max}$ values in the range 5.5–14 h being determined (Table 2). Both the $C_{max}$ and $AUC_{(0-48\ h)}$ were related to the dofetilide P-CAP doses administered, but were not dose proportional.

Inter-individual variability in plasma dofetilide levels was similar from solution and P-CAP treat-

ments. Among pharmacokinetic parameters, variability in $C_{max}$, $T_{max}$ were similar from solution and P-CAP, but variability in $AUC_{(0-48\ h)}$ values tend to be greater for the P-CAP administrations (Tables 1 and 2).

### 3.3. Correlation of pharmacokinetic and scintigraphic assessment

Dispersion of the marker was easy to ascertain in sequential scintigraphic images although since blood sampling and imaging are not carried out simultaneously, there is naturally a small time shift error of no more than $\pm 0.25$ h associated with measurements. Good concordance was noted for the observed release of activity in 24/27 subjects available for analysis, with a mean scintigraphic release time of $5.3 \pm 1.5$ h. In three subjects, blood levels were detected prior to visualisation of scintigraphic dispersion. Fig. 3 shows a typical pattern of release for a subject who had been administered P-CAP containing 0.5 mg of dofetilide.

Although absorption of dofetilide from solution dose was immediate and rapid, absorption from P-CAP did not occur until after the expected approximately 5 h, by which time the dosage form was dispersed to various GI tract sites. Absorption of dofetilide from the P-CAP was observed from all GI sites, however, absorption was generally prolonged from distal sites. Where P-CAP doses were released in the proximal intestine, the observed plasma profiles were generally more consistent with the data for the oral solution (Fig. 4).

The extent of absorption from the different GI tract sites for P-CAP is compared to the oral solution (Table 3) following normalisation of the P-CAP AUC values to equivalent 1.0 mg dofetilide doses. The data show a reduction in bioavailability of dofetilide from P-CAP irrespective of GI tract site of release, with release in the colon showing lowest bioavailability, indicating that the overall absorption of dofetilide was less efficient for the time-delayed P-CAP formulations than from solution.

## 4. Discussion

Low and prolonged levels of dofetilide following P-CAP administrations imply that either release of drug from the preparations was not instantaneous following capsule opening, or that absorption of dofetilide from the distal regions of the intestinal tract is less efficient than from the stomach and proximal small intestine. In part this may be due to sluggish agitation in the distal gut which compounds the loss of bioavailability due to a reduced surface area and decreased paracellular transport.

Scintigraphic images from the study show that when the unit releases in the stomach, small intestine or ICJ, there is a marked increase in dispersion of the marker compared to when the unit releases in the ascending or transverse colon. This leads to a trend of increased dofetilide absorption from those proximal sites as illustrated in Table 3. In one subject the unit remained in the stomach for a prolonged period of time. This observation is not unusual and reflects the absence of migrating myoelectric potentials (housekeeper waves) when subjects are fasted. The rhythm of Phase III is usually established by late mid-morning but can be erratic. The subsequent intake of a lunchtime meal will prevent the emptying of large non-disintegrating objects, such as the size 0 capsule employed in this study.

Table 1
Mean ($\pm$ S.D.) pharmacokinetic parameter values from individual plasma dofetilide profiles following 1.0 mg solution oral dose ($n = 10$)

| $C_{max}$ (ng/ml) | $T_{max}$ (h) | $AUC_{(0-48\ h)}$ (ng h/ml) | $T_{1/2}$ (elim) (h) | $r$ |
|---|---|---|---|---|
| 6.4 (0.8) | 1.7 (0.4) | 74.7 (10.8) | 6.0 (0.8) | 0.97 (0.04) |

$r$ = Correlation coefficient between actual dofetilide plasma profiles and computer generated profiles based on one compartment pharmacokinetic model.

Table 2
Pharmacokinetic parameter values ( ± S.D.) for Pulsincap™ formulations as a function of dose of dofetilide and site of release in the GI tract

| Dose (mg) | Site of release | Number of subjects | $C_{max}$ (ng/ml) | $T_{max}$ (h) | $AUC_{(0-48\ h)}$ (ng h/ml) |
|---|---|---|---|---|---|
| 0.25 | SI | 5 | 1.16 (0.64) | 8.0 (3.66) | 19.1 (8.39) |
| 0.25 | ICJ | 2 | 1.50 (0.14) | 5.5 (0) | 17.7 (3.75) |
| 0.25 | AC | 3 | 0.84 (0.53) | 10.0 (3.46) | 16.4 (5.49) |
| 0.5 | SI | 2 | 1.02 (0.95) | 14.0 (8.49) | 15.1 (7.91) |
| 0.5 | ICJ | 4 | 1.88 (1.02) | 7.25 (2.22) | 29.7 (9.12) |
| 0.5 | AC | 3 | 0.74 (0.17) | 13.3 (7.02) | 21.9 (4.30) |
| 1.0 | Stomach | 1 | 5.70 (0) | 14.0 (0) | 60.4 (0) |
| 1.0 | SI | 2 | 2.20 (1.55) | 12.0 (5.66) | 34.6 (12.16) |
| 1.0 | ICJ | 1 | 1.60 (0) | 14.0 (0) | 43.8 (0) |
| 1.0 | AC | 4 | 1.92 (1.16) | 12.0 (2.83) | 35.5 (21.0) |

The drug formulation employed in this study comprises dofetilide distributed onto a soluble excipient that becomes exposed to GI tract fluid after the capsule opens. As fluid enters, dofetilide may dissolve and either empty rapidly from the capsule resulting in a high $C_{max}$ and a short $T_{max}$ (e.g. at upper GI tract sites where motility and fluid volume is maximised and viscosity minimised) or, alternatively, may diffuse further into the capsule and become dispersed throughout the sucrose excipient and released only progressively, resulting in a lower $C_{max}$ and a prolonged $T_{max}$ (e.g. at lower GI tract sites where motility is reduced and fluid is less available and more viscous). In other studies with P-CAP preparations, in contrast to the soluble excipient fill employed here, the use of rapidly expansive excipient fills have been shown to be highly effective in expelling drug from the opened capsule (Stevens et al., 1999).

With the P-CAP configuration evaluated in this study it is possible that in the colon there is insufficient water to cause rapid dissolution and additionally the sluggish stirring provided by the haustral movements may limit dispersion of the fill. Similarly, the importance and difficulties surrounding the dissolution process in the low-fluid environment within the colon have been highlighted by Takaya et al. (1998) with studies on rupturable capsule formulations.

In other studies with the P-CAP dosing form, we set out to deliver more distally and in order to accomplish this the unit was modified by attaching the drug formulation to the back of the hydrogel plug such that it was pulled out during plug ejection. This approach allowed the mapping of regional differences in quinine absorption (Hebden et al., 1999b) and to investigate the effects of manipulating lumenal water on quinine absorption in the colon (Hebden et al., 1999a). These data, like those presented in the present study show that pulse delivery more distally may result in a diminution in the extent of absorption. However, whether this arises because of reduced permeability of the drugs concerned in the colon or of impeded dispersion from the formulation, remains to be determined.

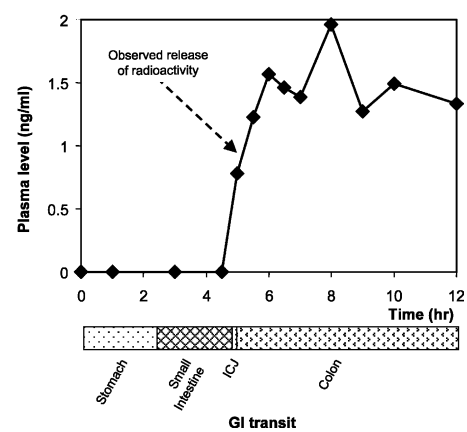


Fig. 3. Pharmacokinetic profile, GI transit and scintigraphic release in one subject.

Table 3
Dofetilide bioavailability as a function of GI tract site for solution and Pulsincap™ formulations

| Formulation | Number of subjects | Site of release | [a]AUC ng h/ml ( ± S.D.) | Relative bioavailability |
|---|---|---|---|---|
| Solution | 10 | Stomach | 74.7 (10.8) | 1.0 |
| P-CAP | 1 | Stomach | 60.4 (0) | 0.81 |
| P-CAP | 9 | SI | 56.8 (33.9) | 0.76 |
| P-CAP | 7 | ICJ | 55.3 (25.8) | 0.74 |
| P-CAP | 10 | Colon | 32.4 (26.7) | 0.43 |

[a] AUC normalised to equivalent 1 mg doses.

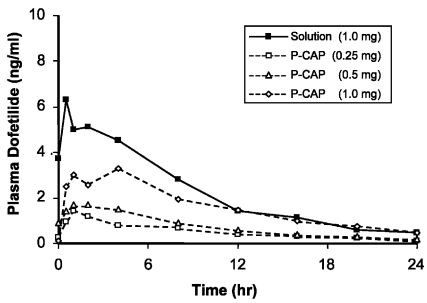


Fig. 4. Dofetilide plasma profiles in a single subject with Pulsincap™ doses released in small intestine (normalised for time 0 = time of first appearance of drug in plasma).

In spite of these reservations, the data obtained from the study in human volunteers demonstrate that the Pulsincap™ delivery system has a role as a convenient probe device and is capable of providing time-delayed release of drug substance within the GI tract. Utilising this approach coupled with gamma scintigraphy, pharmacokinetic parameters can be explored from a range of GI tract sites in man in a non-invasive manner.

## References

Antonin, K.H., 1993. Other methods in studying colonic drug absorption. In: Bieck, P.R. (Ed.), Colonic Drug Absorption and Metabolism. Marcel Dekker, New York, pp. 89–107.

Bakhshaee, M., Binns, J.S., Stevens, H.N.E., Miller, C.J., 1992. Pulsatile drug delivery to the colon monitored by gamma scintigraphy. Pharm. Res. 9 (suppl.), F230.

Barr, W.H., Zola, E.M., Chandler, E.L., Hwang, S.M., Tendolkar, A.V., Shamburek, R., Parker, B., Hilty, M.D., 1994. Differential absorption of amoxicillin from the human small and large intestine. Clin. Pharmacol. Ther. 56, 279–285.

Binns, J.S., Bakhshaee, M., Miller, C.J., Stevens, H.N.E., 1993. Application of a pH independent PEG based hydrogel to afford pulsatile drug delivery. Proc. Int. Symp. Control. Rel. Bioact. Mater. 20, 226–227.

Binns, J.S., Stevens, H.N.E., McEwan, J., Pritchard, G., Brewer, F.M., Clarke, A., Johnson, E.S., McMillan, I., 1996. The tolerability of multiple oral doses of Pulsincap™ capsules in healthy volunteers. J. Control. Rel. 38, 151–158.

Chan, K.K.H., Buch, A., Glazer, R.D., John, V.A., Barr, W.H., 1994. Site-differential gastrointestinal absorption of benazepril hydrochloride in healthy volunteers. Pharm. Res. 11, 432–437.

Connor, A.L., Wray, H.A., Voith, B., Voight, U., Nagelschmitz, J., Kuhlmann, J., Wilding, I.R., 2001. Using the Enterion capsule to investigate the absorption of Faropenem Daloxate delivered in particulate form from different sites of the gastrointestinal tract. AAPS Pharm. Sci. 3 (3), s5125.

Fuhr, U., Staib, A.H., Harder, S., Becker, K., Liermann, D., Schollnhammer, G., Rod, I.S., 1994. Absorption of ipsapirone along the human gastrointestinal tract. Brit. J. Clin. Pharmacol. 38, 83–86.

Gardner, D., Casper, R., Leith, F., Wilding, I.R., 1997. Non-invasive methodology for assessing regional drug absorption from the gastrointestinal tract. Pharm. Technol. Eur. 9, 46–53.

Harder, S., Fuhr, U., Beermann, D., Staib, A.H., 1990. Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the hf-capsule. Brit. J. Clin. Pharmacol. 30, 35–39.

Hebden, J.M., Gilchrist, P.J., Perkins, A.C., Wilson, C.G., Spiller, R.C., 1999a. Stool water content and colonic drug absorption: contrasting effects of lactulose and codeine. Pharm. Res. 16, 1254–1259.

Hebden, J.M., Wilson, C.G., Spiller, R.C., Gilchrist, P.J., Blackshaw, P.E., Frier, M., Perkins, A.C., 1999b. Regional differences in quinine absorption from the undisturbed human colon assessed using a timed release delivery system. Pharm. Res. 16, 1087–1092.

Krögel, I., Bodmeier, R., 1998. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm. Res. 15, 474–481.

Lambert, A., Vaxman, F., Crenner, F., Wittmann, T., Grenier, J.F., 1991. Autonomous telemetric capsule to explore the small bowel. Med. Biol. Eng. Comput. 29, 191–196.

McNeil, M.E., Rashid, A., Stevens, H.N.E., 1994. Drug dispensing device. US Patent 5 342 624.

Olsson, B., Wagner, Z.G., Mansson, P., Ragnarsson, G., 1995. A gamma scintigraphic study of the absorption of morphine from controlled-release tablets. Int. J. Pharm. 119, 223–229.

Parr, A.F., Sandefer, E.P., Wissel, P., McCartney, M., McClain, C., Ryo, U.Y., Digenis, G.A., 1999. Evaluation of the feasibility and use of a prototype remote drug delivery capsule (RDDC) for non-invasive regional drug absorption studies in the GI tract of man and beagle dog. Pharm. Res. 16, 266–271.

Rashid, A., 1990. Dispensing Device. European Patent 0 384 642.

Read, N.W., Aljanabi, M.N., Bates, T.E., Barber, D.C., 1983. Effect of gastrointestinal intubation on the passage of a solid meal through the stomach and small intestine in humans. Gastroenterology 84, 1568–1572.

Ross, A.C., MacRae, R.J., Walther, M., Stevens, H.N.E., 2000. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J. Pharm. Pharmacol. 52, 909–916.

Smith, D.A., Rasmussen, H.S., Stopher, D.A., Walker, D.K., 1992. Pharmacokinetics and metabolism of dofetilide in mouse, rat, dog and man. Xenobiotica 22, 709–719.

Staib, A.H., Beerman, D., Harder, S., Fuhr, U., Liermann, D., 1989. Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote control drug delivery device (HF-capsule). Am. J. Med. 87, 66S–69.

Stevens, H.N.E., Rashid, A., Bakhshaee, M., 1995. Drug Dispensing Device. US Patent 5 474 784.

Stevens, H.N.E., Rashid, A., Bakhshaee, M., Binns, J.S., Miller, C.J., 1999. Expulsion of material from a delivery device. US Patent 5 897 874.

Takaya, T., Niwa, K., Muraoka, M., Ogita, I., Nagai, N., Yano, R., Kimura, G, Yoshikawa, Y, Yoshikawa, H, Takada, K., 1998. Importance of dissolution process on systemic availability of drugs delivered by colon delivery system. J. Control. Release 50 (1–3), 112–122.

Vidon, N., Pfeiffer, A., Godbillon, J., Rongier, M., Gauron, S., Hirtz, J., Bernier, J.J., Bidois, J.P., 1989. Evaluation of the gastric absorption and emptying of drugs under various pH conditions using a simple intubation method: application to diclofenac. Brit. J. Clin. Pharmacol. 28, 121–124.

Walker, D.K., Herne, G.W., Arrowsmith, J.E., Cross, P.E., Kaye, M.B., Smith, D.A., Stopher, D.A., Wild, W., 1991. Measurement of the class III antiarrhythmic agent UK-68 798 in plasma by radioimmunoassay. J. Pharm. Biomed. Ann. 9, 141–149.

Wilding, I.R., Davis, S.S., Bakhshaee, M., Stevens, H.N.E., Sparrow, R.A., Brennan, J., 1992. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Pharm. Res. 9, 654–657.

Wilson, C.G., Washington, N., 1988. Assessment of disintegration and dissolution of dosage forms in vivo using gamma scintigraphy. Drug Dev. Ind. Pharm. 14, 211–271.

Wilson, C.G., Washington, N., Greaves, J.L., Washington, C., Wilding, I.R., Hoadley, T., Sims, E.E., 1991. Predictive modelling of the behaviour of a controlled-release buflomedil HCl formulation using scintigraphic and pharmacokinetic data. Int. J. Pharm. 72, 79–86.

Wilson, C.G., Bakhshaee, M., Stevens, H.N.E., Perkins, A.C., Frier, M., Blackshaw, P.E., Binns, J.S., 1997. An evaluation of a gastro-resistant pulsed release delivery system (Pulsincap) in man. Drug Delivery 4, 201–206.