Review

Gut instincts: Explorations in intestinal physiology and drug delivery

Emma L. McConnell, Hala M. Fadda, Abdul W. Basit*

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

A R T I C L E   I N F O

Article history:
Received 1 February 2008
Received in revised form 3 May 2008
Accepted 6 May 2008
Available online 20 May 2008

Keywords:
Gastrointestinal tract
Dissolution
Oral drug delivery
Colonic delivery
Inflammatory bowel disease
Biopharmaceutics
Large intestine
Modified release
In vitro in vivo correlation
Vaccination

A B S T R A C T

We need to look beyond our gut instincts to use information on “simple” intestinal physiological parameters as they have been presented to us in the past. Here we present a discussion on such parameters, old and new, and ask how much we really understand them. Behaviour of drugs and delivery systems in the intestine depends on many physiological factors including fluid volume, fluid composition, transit, motility, bacteria and pH, which are further influenced by food, gender and age. These are often considered well understood, but their true variability and idiosyncrasies are not fully appreciated or utilised in intestinal dosage form design or in vitro testing. There are still many unknowns in these areas. The distal gut especially has been neglected, and the influence of disease is often ignored. As pharmaceutics moves forward into the molecular era an understanding of the role of cellular mechanisms of transporters and metabolic enzymes is important, but the basics must not be forgotten. This discussion on intestinal physiology is utilised to address those areas which require further research and understanding, and new technologies are highlighted. Better understanding of the fundamental information available can open new avenues for research and pave the way for the future of gastrointestinal drug delivery.

© 2008 Elsevier B.V. All rights reserved.
1. Introduction

Medication has been given by the oral route for many thousands of years; Paleolithic and Neolithic man are thought to have valued the medicinal qualities of herbs, and the first known medical text, from Mesopotamia 2100 b.c., describes aqueous and oil extracts, and infusions of wine and beer (Cowen and Helfand, 1990). The oral route is still preferred today, and over eighty percent of the best-selling pharmaceutical products are given by mouth (Lennernas and Abrahamsson, 2005). Oral drug delivery has come a long way since its origins in history, and attention has now turned towards modifying and manipulating oral dosage forms to exploit the conditions of the gastrointestinal tract to deliver drugs in different ways. The increasing use of modified release dosage forms, pro-drugs, and low solubility or low permeability drug candidates mean that drug or dosage forms are becoming more likely to reach the lower regions of the gut, and are subject to the fluctuating conditions of almost the entire gastrointestinal tract.

The extensive use of oral medication implies simplicity. It is a common misconception that gut physiology is well understood. Often the complexity and variability of gut physiology is underestimated, with only one or two variables being considered in dosage form design and drug targeting. Although strides have been made towards understanding the conditions and mechanisms in the healthy gut, there are gaps in our knowledge, and the lower gut is largely ignored. Even more significant is the lack of understanding or appreciation of the gastrointestinal environment in the disease state. We cannot design functional dosage forms which behave in a reproducible manner without a clear understanding of the conditions to which they will be subjected. Understanding of the intestinal environment will not only allow better dosage form design, but improved in vitro and pre-clinical in vivo testing, better in vitro in vivo correlations, as well as opening new avenues for oral drug delivery. Here we aim to highlight some of the important and sometimes overlooked features; we address some misconceptions, and suggest areas for further research. The stomach is much more extensively studied than the lower gut and although we include it for comparison purposes in some instances this article will mainly focus on some important aspects of small intestinal and colonic physiology and technologies for delivering drugs to the lower gut.

2. Water, water, everywhere? The ramifications of gastrointestinal fluid in the gut

2.1. Fluid volumes

A value for post-mortem fluid volume in the gastrointestinal tract was measured in the 1950s (Gotch et al., 1957) (Table 1) and the total colonic water was measured by Cummings et al. (1990) (Table 1). These authors report mean values of 118 ml in the stomach and 212 ml in the small intestine (Gotch et al., 1957) and 187 ml in the large intestine (Cummings et al., 1990). Although gastrointestinal fluid is essential for disintegration, dispersion, dissolution or absorption in the oral drug delivery process, these values remain largely ignored in the literature and are often not accounted for in either design or testing of dosage forms. In recent years, Schiller and co-workers quantified the free fluid in the gut, i.e. water not bound to digesta, using magnetic resonance imaging and found that the free water content of the gut lumen is not homogeneously distributed and, in fact, exists as fluid pockets (Schiller et al., 2005). Dosage form disintegration may rely heavily on whether a formulation is in one of these fluid pockets or not. A high variability was demonstrated, for example a modified release dosage form could be exposed to anything from 1 to around 100 ml of free fluid in the colon.

2.2. Fluid composition

The total fluid volume is not the only influential factor on dissolution; we need to consider the composition of the fluid in question. Gastrointestinal fluid is complex, dynamic and fluctuating (Table 1) which contrasts with the simple acid and phosphate buffer solutions used for in vitro testing. It has been well documented that dissolution rates of ionisable drugs (Mooney et al., 1981; Ozturk et al., 1988; Aunins et al., 1985; Ramtola and Corrigan, 1989) and enteric-coated dosage forms (Ozturk et al., 1988) are influenced by buffer capacity and species. In vitro in vivo correlations of drug release from solid dosage forms may be greatly improved by defining the dissolution environment simply in terms of ionic composition. For example, using physiological Hank’s and Kreb’s bicarbonate buffers (which simulate the ionic composition of the jejunal and ileal fluids, respectively) gave better reflections of in vivo disintegration times of enteric-coated systems, and were more discriminative than compendial phosphate buffers (Fadda and Basit, 2005; Ibebewe et al., 2006a). Hank’s and Kreb’s media have a buffer capacity comparable to that of intestinal luminal fluids and have been found to provide a good surrogate for solubility measurement of ionics (Fadda and Basit, 2007). McNamara et al. (2003) showed that different buffers including bicarbonate media with various partial pressures of CO₂ significantly influenced the intrinsic dissolution of ionisable drugs. Boni et al. (2007) also showed different dissolution profiles of modified release formulations of a basic drug in bicarbonate and phosphate buffers. Surface tension also affects drug dissolution through its influence on wetting. The surface tension of gastric fluid has been characterised to be in the range of 28–45mN/m (Efentakis and Dressman, 1998; Pedersen et al., 2000) and can be mimicked through the addition of pepsin and/or surfactants to HCl (Aubur et al., 2008; Vertzoni et al., 2005). The effects of bile salts and phospholipid surfactants on the solubility and dissolution of poorly water-soluble drugs have been extensively explored (Dressman et al., 1998). Inclusion of these into in vitro dissolution fluids has been advocated (Nicolaides et al., 1999) with mixed results (Kalantzi et al., 2006; Persson et al., 2005; Fadda and Basit, 2007). Fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF) incorporate bile salts and phospholipids. Updated versions of these have recently been developed with particular attention to simulating different phases of postprandial digestion (Janratid et al., 2008). Two of the lipid digestion products, glyceryl monooleate and sodium oleate, were further incorporated in these media. More attention still needs to be paid, however, to mimicking the other bile salts in the gut lumen. For example, FaSSIF contains sodium taurocholate (a trihydroxy acid) as its only bile salt and this is only twenty percent of the in vivo bile salts (di- and trihy-
Table 1
Characterisation of gastrointestinal fluid in man

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
<th>Large intestine</th>
<th>Proximal colon</th>
<th>Distal colon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total fluid volume (ml)</strong></td>
<td>PM 118 ± 82¹</td>
<td>212 ± 101²</td>
<td>54 ± 41³</td>
<td>105 ± 72⁴</td>
<td>187²</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Free fluid volume (ml)</strong></td>
<td>Fed 45 ± 18</td>
<td>54 ± 41³</td>
<td>105 ± 72⁴</td>
<td>–</td>
<td>11 ± 26⁴</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 35.6 ± 5.9⁵</td>
<td>32.3⁶</td>
<td>28 ± 17⁶</td>
<td>–</td>
<td>28 ± 17⁶</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Surface tension (mN/m)</strong></td>
<td>3.6 ± 5.9⁵</td>
<td>33.6 ± 5.9⁵</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Bile salt concentration (mM)</strong></td>
<td>Fed 0.06⁸</td>
<td>11.2⁸</td>
<td>8 ± 0.1³</td>
<td>2–10³</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 0.2 ± 0.2⁸</td>
<td>0.57–5.1¹¹</td>
<td>2 ± 0.2³</td>
<td>2.9 ± 2.9¹⁰</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Bile flow rate (ml/min/kg)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Acid output (mEq/hr)</strong></td>
<td>Fed 0.06³</td>
<td>8 ± 0.2³</td>
<td>11.2 ± 5.1²</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 0.2 ± 0.2³</td>
<td>0.57–5.1¹¹</td>
<td>2 ± 0.2³</td>
<td>2.9 ± 2.9¹⁰</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Phospholipids (mM)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>pH³⁴</strong></td>
<td>Fed 1.0–2.5</td>
<td>–</td>
<td>6.6 ± 0.5</td>
<td>7.5 ± 0.5</td>
<td>6.4 ± 0.6</td>
<td>7.0 ± 0.7</td>
<td>–</td>
</tr>
<tr>
<td><strong>Bacterial Levels (CFU/g contents)</strong></td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Redox potential (mV)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Bicarbonate (mM)</strong></td>
<td>–</td>
<td>6.7²¹¹</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Phosphate (mM)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Potassium (mM)</strong></td>
<td>68 ± 29¹⁰</td>
<td>–</td>
<td>4.9 ± 0.3³</td>
<td>4.6 ± 0.3³</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Sodium (mM)</strong></td>
<td>102 ± 28¹⁰</td>
<td>126 ± 10⁹</td>
<td>125 ± 12³</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Chloride (mM)</strong></td>
<td>68 ± 29¹⁰</td>
<td>142 ± 13⁹</td>
<td>140 ± 0.6³</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Magnesium (mM)</strong></td>
<td>0.6 ± 0.2²</td>
<td>0.5 ± 0.3³</td>
<td>4.2³</td>
<td>–</td>
<td>4.2³</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Ionic strength (mM)</strong></td>
<td>6 ± 0.2²</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Buffer capacity (mmol/L/pH unit)</strong></td>
<td>Fed 6 ± 0.2²</td>
<td>6 ± 0.2²</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 6 ± 0.2²</td>
<td>6 ± 0.2²</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Short chain fatty acids (mmol)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Amylase (U/ml)</strong></td>
<td>Fed 14–28⁶</td>
<td>18–30⁶</td>
<td>2.4–2.8⁹</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 6 ± 0.2²</td>
<td>6 ± 0.2²</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Lipase (U/ml)</strong></td>
<td>Fed 400–1000³</td>
<td>500–1500²⁷,²⁸,³⁰</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 400–1000³</td>
<td>500–1500²⁷,²⁸,³⁰</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Trypsin (U/ml)</strong></td>
<td>Fed 20–50³</td>
<td>50–100³</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Fasted 20–50³</td>
<td>50–100³</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Gas volume (ml)</strong></td>
<td>36 ± 12</td>
<td>4³</td>
<td>–</td>
<td>–</td>
<td>182 ± 26⁻</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: PM = post-mortem, *indicates that data was not found; ¹indicates the value represents that the whole small intestine, or no differentiation was made in the study; ²this value is for the whole colon; ³represents a value for the duodenum and jejunum; ⁴this value is reported at 206 ml in the original reference but our recalculation of the results shows a mean of 212 ml.

1Gotch et al. (1957).
2Cummings et al. (1990).
3Schiller et al. (2005).
5Pedersen et al. (2000a).
6Kalantzi et al. (2006a).
7Persson et al. (2005).
8Rhodes et al. (1969).
9Northfield and McColl (1973).
10Lindahl et al. (1997).
11Perez de la Cruz Moreno et al. (2006).
12Martinez et al. (2002).
14Evans et al. (1988).
16Bernhardt and Knoke (1997).
17Stirrup et al. (1990).
18Repishiti et al. (2001).
20Phillips and Summerskill (1967).
21Banwell et al. (1971).
22Wrong et al. (1965).
24Yadda and Basit (2007).
26Holmwood et al. (1996).
28Bozkurt et al. (1988).
29Braganza et al. (1978).
30Keller et al. (1997).
31MacFarlane and Eniglyst (1986).
32DiMagno et al. (1977).
33Mearin et al. (2006).
34Wrong et al. (1997).
droxyacids) [Vertzoni et al., 2005]. Lecithin, also present in FaSSIF and FeSSIF, is not the only phospholipid in small intestinal fluids, with lysolecithin (a hydrolysis product of lecithin) additionally being found (Ammon et al., 1983). This has a different solubilising capacity. The pancreatic enzyme levels in the gut are also a significant factor to be considered. Pancreatic enzyme levels are variable and USP recommendations for dissolution testing do not reflect the in vivo scenario. Levels of digestive enzymes increase markedly following meal consumption (Table 1).

2.3. Fluid in disease

The in vivo fluid volumes and composition are influenced by pathology. For example, constipation results from increased water resorption in the gut leading to more viscous or solid colonic contents. Its aetiology is usually related to delayed transit or obstruction to defecation (Camilleri et al., 1994) and its presence may make drug dispersal or dissolution problematic. Chronic diarrhoea is common in the active phase of inflammatory bowel disease (often abating on remission), and is implicated in 30–60% of North American and European AIDS patients and in nearly 90% of AIDS patients in developing countries (Dancygier, 1998). The pathophysiology of diarrhoea is linked with colonic sensitivity (Rao et al., 1987; Camilleri and Ford, 1998), sodium and water absorption (Allan et al., 1975; Greig and Sandle, 2000) and leaky tight junctions (Seidler et al., 2006). Crohn's patients suffering from inflammation or resection of the terminal ileum, or patients with impaired gall bladder or liver function can experience fat or bile salt malabsorption (McNeil et al., 1982; Akerlund et al., 1994) which potentially has serious implications for drug bioavailability of lipophilic molecules.

3. How variable are gastrointestinal transit times?

3.1. Transit in the intestine

The various idiosyncrasies of gastric retention and emptying have been studied extensively and it has been stated categorically that “almost everything seems to affect gastric emptying” (Olsson and Holmgren, 2001). In contrast, the small intestinal transit time is assumed to be independent of external influences, and more consistent. The small intestine transit time of dosage forms is almost invariably quoted at 3–4 h (Davis et al., 1986), and a meta-analysis of transit data in the small intestine showed no difference between tablets, pellets and liquids (Davis et al., 1986). This is however, a mean value from pooled data with different methodologies, and is often taken out of context. In this study the actual values range from 0.5 to ~9.5 h. Coupe et al. (1991) measured the variability in small intestinal transit times of multiple- and single-unit systems; the range for pellets was 2.2–5.9 h and that for an 11.5 mm tablet was 0.9–6.2 h. Intra-subject variability was also observed. The intra-subject variability is further exemplified by data generated by our group, in which non-disintegrating ethylcellulose-coated pellets (1–1.4 mm) were given to one subject on eight separate occasions (unpublished data). The average transit time is indeed 3.2 h, (1–1.4 mm) were given to one subject on eight separate occasions group, in which non-disintegrating ethylcellulose-coated pellets was 0.9–6.2 h. Intra-subject variability was also observed. The intra-subject variability is further exemplified by data generated by our group, in which non-disintegrating ethylcellulose-coated pellets (1–1.4 mm) were given to one subject on eight separate occasions (unpublished data). The average transit time is indeed 3.2 h, (1–1.4 mm) were given to one subject on eight separate occasions group, in which non-disintegrating ethylcellulose-coated pellets was 0.9–6.2 h. Intra-subject variability was also observed.

The small intestinal transit of dosage forms is much more complex than simply being a function of intestinal motility and flow. It is not continuous; using magnetic marker monitoring studies Weitschies et al. (2005) were able to describe the movement of a non-disintegrating capsule along the tract. In the duodenum fast passage was observed, with a capsule traversing the length in anything from a few seconds up to several minutes. Retro-propulsion was demonstrated; in one case back into the stomach. In one individual on five separate occasions very different intestinal transit profiles were seen with varying periods of movement and stasis (Fig. 2).

Like the small intestine, movement through the colon is not continuous, and in the transverse colon, the dosage forms were observed to be often at rest; spending 5–30 min periods with no lower bioavailability from enteric-coated erythromycin beads given 30 min before food. This was related to a faster small intestinal transit time of the dosage form.

Dose form transit is influenced by intestinal motility. In the fasted state, motility is controlled by the migrating myoelectric complex (MMC), which cycles over 90–120 min. Interestingly the MMC does not only start at the stomach, but at various points along the GI tract including the oesophagus and small intestine (Kellow et al., 1986) which may help account for the observation that single unit dosage forms often empty in times far in excess of the expected emptying time of less than two hours. The incidence of MMCs is also different in various regions of the gut; the numbers of MMCs in the jejunum was arbitrarily assigned to be 100% and in relation to that the mean incidence of MMCs in the lower oesophagus, gastric antrum, duodenum, proximal ileum and terminal ileum was determined to be 56%, 74%, 94%, 36% and 9%, respectively (Kellow et al., 1986). The correlations between dosage form transit and the MMC were proposed in the 1980s when it was observed that the average speed of a non-disintegrating capsule through the small intestine (excluding the duodenum which was too fast to measure) was between 4.2 and 5.6 cm/min (Kaus et al., 1984) which corresponded to the reported velocity of the MMC down the intestine of 4.7 cm/min (Kerlin and Phillips, 1982). The transit of a dosage form may also be influenced by intestinal flow; in the fasted state the mean intestinal flow rates for all phases of the MMC are 0.73 ml/min in the jejunum and 0.33 ml/min in the ileum. Postprandially, these flow rates are significantly accelerated to 3.0 and 2.35 ml/min, respectively (Kerlin et al., 1982). Currently, it is not clear exactly how much influence these flow patterns have on dosage form transit.

The small intestinal transit of dosage forms is much more complicated than simply being a function of intestinal motility and flow. It is not continuous; using magnetic marker monitoring studies Weitschies et al. (2005) were able to describe the movement of a non-disintegrating capsule along the tract. In the duodenum fast passage was observed, with a capsule traversing the length in anything from a few seconds up to several minutes. Retro-propulsion was demonstrated; in one case back into the stomach. In one individual on five separate occasions very different intestinal transit profiles were seen with varying periods of movement and stasis (Fig. 2).
be exploited to improve therapeutics. Many diseases are known to
involve circadian rhythms, which represent an aspect of the physiology which can
affect gastrointestinal motility (Rao et al., 2001). Circadian rhythms are a result of the
defaecation times, and other factors such as age and sex. Bowel movements are
usually included in the defecation event. Defaecation occurs in the morning in many
volunteers, which ranged from 5.1 to 58.3 h (median 27.4 h) (John et al., 1991) but values in excess of 70 h have been described (Rao et al., 2004) with men having significantly shorter transit times than women (Metcalf et al., 1987; Buhmann et al., 2007). Similar gender differences were reported in small-bowel transit and gastric emptying (Sadik et al., 2003). This introduces an interesting physiological discussion point: how much is actually known about the effects of gender on drug and dosage form behaviour? It is generally acknowledged in the literature and by the regulatory authorities that there are some differences in drug behaviour between men and women, but the full implications of these are not yet established.

3.2. Total transit

Factoring in variability in the stomach, small intestine and large
intestine, transit through the gut can range from a few hours, to several
days (Wilding, 2001). The OROS® system (non-disintegrating osmotically driven tablets) showed total transit times in healthy volunteers, which ranged from 5.1 to 58.3 h (median 27.4 h) (John et al., 1985). Most of the variability tends to be associated with the colon (Wilding, 2001). The motility and transit in the colon is highly influenced by defaecation time; a study analyzing pooled data from administrations of the OROS® showed that morning doses had transits clustered at 24 and 36 h, and nighttime administration showed transits clustered around 12 and 36 h (Sathyam et al., 2000). They thus related the total transit time to a combination of two factors; the defaecation frequency and the likelihood of it being included in the defaecation event. Defaecation occurs in the morning in many subjects, and the nighttime administrations may be included in the next morning’s bowel movement or, more likely, on the following morning (36 h).

Although this “clustering” of transit times described with the
OROS system is a result of defaecation times, there are other circadian aspects to gastrointestinal motility (Rao et al., 2001). Circadian rhythms represent an aspect of the physiology which can be exploited to improve therapeutics. Many diseases are known to be worse at certain times to the day (Smolensky and Haus, 2001) such as high blood pressure, arthritis or asthma, and chronotherapy is being exploited for the treatment of such conditions which would utilise modified release technology. In terms of gastrointestinal physiology, there are changes over a 24 h period in gastric acid secretion and motility. In patients with functional constipation there was a significantly lower contractile response to morning awakening compared to controls (Zhang et al., 2007) and gastric emptying rates significantly longer with solids foods in the evening (Goo et al., 1987). Melatonin may have a role in the secretion of pepsin and hydrochloric acid, as well as influencing the activity of the myoelectric complexes (Bubenik, 2001). Small changes in these physiological functions can lead to marked differences in drug and dosage form behaviour.

The variability of total transit proves problematic in drug delivery, especially where modified release dosage forms are being used. This was exemplified by work in which the plasma concentration of 4-aminosalicylic acid (4-ASA) after administration of a colon-specific dosage form was assessed in human volunteers (Tuleu et al., 2002) (Fig. 3). In one subject, the coated capsule arrived in the colon at around 7 h, and drug was measured in the plasma over the next 5 h. In another volunteer the gastrointestinal transit was very short; the capsule arrived at the colon at 3 h, and was voided at less than 6 h. The rapid colonic transit in this volunteer prevented the breakdown of the dosage form, and no drug was observed in the plasma.

3.3. Transit in disease

Patients with irritable bowel syndrome often have accelerated
intestinal transit times (Vassallo et al., 1992) and motor disorders were observed in the small intestine of 26 of 35 patients with inactive Crohn’s disease (reduced phase II contractions, increased incidence of propagated single and clustered contraction) (Amnese et al., 1997) which may make this type of problem more commonplace in clinical situations. Patients with active ulcerative colitis have also been found to have significantly faster colon transit than controls (24.3 h vs. 51.7 h) (Hebden et al., 2000). Interestingly,
they also showed an asymmetric distribution of material in the colon. Amberlite™ resin (to mimic drug-loaded powder/pellets) was dosed in an Eudragit S (colon-targeted) capsule to these ulcerative colitis patients, and to control subjects. In the control subjects, 69% of the dosed Amberlite™ was observed to be in the proximal colon after release in the large intestine, and the remaining in the distal colon. In ulcerative colitis patients, 91% was distributed in the proximal colon. This exaggerated asymmetry of dosage form dispersion has implications for ulcerative colitis affecting the distal regions, resulting in reduced exposure of the site to drug. This goes some way towards explaining the fact that recent studies have shown that a combination of oral and rectal mesalazine (an anti-inflammatory drug) was more effective than either given alone for distal inflammatory bowel disease (Martel et al., 2005).

Many patients with Crohn’s disease undergo an ileocolic resection (Munkholm et al., 1993). This has been shown to significantly reduce the small intestinal transit time mainly due to the shorter time spent at the ileocolic junction (Fallingborg et al., 1998).

Transit and motility can be further linked with gas volumes and transit. Irritable bowel syndrome (IBS) patients frequently complain of bloating and abdominal distension (Barbara et al., 2004). However, studies showed that the actual gas volume and composition is not higher in patients with ‘excess gas’ complaints compared to controls (Lasser et al., 1975). Gas transit times were found to be longer in symptomatic patients relative to controls (40 ± 6 min vs. 22 ± 3 min) (Lasser et al., 1975). Dosage form may come into contact with gas pockets within the gut, in addition to the fluid pockets described earlier.

3.4. Manipulation of transit

In addition to disease, transit can also be altered by drugs (Kachel et al., 1986; Barone et al., 1994; Reynolds, 1989) and excipients. Polyethylene glycol 400, a solubility enhancing excipient, has been shown at pharmacologically relevant doses to stimulate intestinal motility and accelerate small intestinal transit (Basit et al., 2001, 2002b; Schulze et al., 2003), although this effect was not seen with other excipients of the same class (Schulze et al., 2005, 2006). Two effervescent excipients, mannitol and sodium acid pyrophosphate have exhibited similar effects on transit (Adkin et al., 1995a,b; Koch et al., 1993). These transit effects can have an influence on drug bioavailability (Schulze et al., 2005; Basit et al., 2002b; Adkin et al., 1995c; Ashiru et al., 2008).

Physiological triggers have been investigated to slow transit, for example the ileal brake. This is a feedback mechanism in which lipids and fatty acids in the ileum can slow the transit of luminal contents through the small intestine (Spiller et al., 1984, 1988). This approach has been used to slow the transit of tablets (Dobson et al., 1999). However, in in vivo studies using atenolol, only in some volunteers did the increase in small intestinal transit time led to an increase in drug absorption (Dobson et al., 2002). The authors suggest that other factors such as ileocaecal junction residence time are involved, highlighting the complexities of the physiological processes in the gut, and the importance of considering the interplay between such factors.

Mucoadhesive to the intestinal mucosa could, in theory, normalise the variations in intestinal transit and allow more consistent performance of formulations within and between individuals, improving the overall efficacy of a drug (Varum et al., 2008). Mucoadhesive approaches in the upper gastrointestinal tract have shown a great deal of potential in vivo and in small animal studies (Ch‘ng et al., 1985; Longer et al., 1985; Quan et al., 2008) but success has failed to translate to human studies in the stomach and small intestine (Harris et al., 1990; Sakkinen et al., 2006; Khosla and Davis, 1987). It may be that the in vitro studies used are not appropriate to mimic mucosal conditions in the gastrointestinal tract, and small animal models are unsuitable. This reinforces the point that suitable testing methods need to be developed, with appropriate compositions and mechanical forces, in order to achieve any reliable extrapolation into man. This is true for dissolution models, and for mucoadhesive models such as these, as well as in vivo models.

Lack of success in the upper gastrointestinal tract should not dissuade researchers from further investigations into mucoadhesion. Certainly buccal mucoadhesion has been successful and perhaps the colon still has potential in this area? Colonic mucoadhesion may be more successful than small intestinal or gastric approaches, due to a thicker mucus layer (Strugala et al., 2003) and lower disruptive colonic motility. It also has a lower mucus turnover and sensitivity to mucus secretory stimulus making dosage form mucoadhesion less rate–limited by mucus turnover (Lehr et al., 1991; Rubinstein and Tirosh, 1994; Rubinstein et al., 1997).

4. Is gastrointestinal pH predictable?

4.1. pH in health

The shortcomings of in vitro testing with respect to gastrointestinal fluid volume and composition have been discussed. For reasons of economics or time, researchers choose to use simple buffer systems. One aspect that is invariably controlled in these tests, and based on the reported physiological parameters, is gastrointestinal pH. This has been reported by many authors, and is generally believed to be well characterised and we report the results of Evans et al. (1988) in Table 1, as it is considered to be the most authoritative. However, the most important message from such studies is often overlooked; the pH shows huge variability between people, and a striking example of this is demonstrated in the pH profiles measured by Fallingborg et al. (1989) in 39 healthy individuals in which there can be over two pH units difference at the same site. In addition, the pH of the proximal small intestine, which is often modelled at pH 6.8, has recently been shown to have a mean value of 5.5 (by in situ measurements in the duodenum taken over 48 h (Bratten and Jones, 2006).

In addition to inter-individual variability, there are also potentially marked differences within individuals on different occasions; previous work by our group showed substantial differences in gastrointestinal pH profiles measured 1 week apart, under the same feeding conditions (Ibekwe et al., 2008). An example pH profile, obtained by our research group, for one healthy subject can be seen in Fig. 4 (unpublished results). This was obtained using the Bravo® pH capsule, a radiotelemetric pH-sensitive device which

![Fig. 4. pH profile from one subject using the Bravo® pH capsule. The capsule was given 30 min before food (standard breakfast) and a standard lunch was administered at 4 h (unpublished data).](image-url)
was ingested by the subject. After around 30 min a standard breakfast was ingested, and this can seen as a sustained rise in gastric pH. The pH capsule is retained in the stomach, and food is administered again at 4 h, again seen by the sustained rise in pH. At around 5 h the capsule empties from the stomach, and the intestinal pH can be observed.

4.2. pH changes in disease

The pH in the stomach is influenced by pathophysiological conditions such as hypochlorhydria/achlorhydria (reduced or absent gastric acid secretion) or hypergastrinemia (oversecretion of gastrin and a pH <2) (Arnold, 2007) and AIDS (Lake-Bakaar et al., 1998) by medication such as H2 receptor antagonists and proton pump inhibitors. This has implications for the dissolution and bioavailability of weakly basic drugs; ketoconazole bioavailability was decreased in AIDS patients with raised gastric pH (Lake-Bakaar et al., 1998). Another study looked at the effects of drug-induced achlorhydria (using the proton pump inhibitor omeprazole) and showed a reduction in ketoconazole bioavailability. Interestingly, they were able to improve bioavailability 65% over a control (water) by administration with an acidic beverage (Coca-Cola) (Chin et al., 1995).

The small intestinal pH appears to be unchanged in Crohn’s disease (Ewe et al., 1999; Fallingborg et al., 1998; Press et al., 1998; Raimundo et al., 1992). In the colon, however, lower pH values are seen in disease states (Nugent et al., 2001). For example, Raimundo et al. (1992) reported right colon pH values of 4.7 (±0.72) in acute ulcerative colitis and in other studies a fall in colonic pH to less than 5.5 was found in two out of six patients (Nugent et al., 2000) and a proximal colonic pH as low as 2.3 was detected (Fallingborg et al., 1993). In Crohn’s disease (active and inactive) colonic pH was significantly lower than in healthy age-matched controls, with a mean proximal and distal colonic pH of 5.3 (compared to the mean control pH of 6.8 proximally and 7.2 distally) (Sasaki et al., 1997).

4.3. pH and drug delivery

The pH changes along the intestine have been exploited for the purposes of drug delivery. Enteric coatings are employed to prevent drug release in the stomach. These coatings are generally made from pH-responsive polymers which remain unionised and intact at the low pH of the stomach, but dissolve at the higher pH of the small intestine. The principle has been extended to colonic delivery. The first colon-targeted pH-responsive delivery system was developed by Dew et al. (1982) and comprised a capsule coated with the poly-methacrylic acid methylmethacrylate ester copolymer, Eudragit S (Evonik, Darmstadt, Germany), which has a dissolution threshold of pH 7 and should theoretically dissolve in the distal small intestine. This concept was postulated when it was thought that the intestinal pH increased distally along the gut; it is now known that the pH drops slightly in the colon, and the pH is highest at the ileocaecal junction (Evans et al., 1988). Rather than colon-targeted delivery, this type of pH-responsive delivery described is more accurately referred to as “ileo-colonic” drug delivery, or targeting (Ibekwe et al., 2006b, 2008). This pH-triggered approach formed the basis for the development of Eudragit S-coated mesalazine tablets marketed as Asacol® for ulcerative colitis. This, and other preparations based on the same concept (Mesren, Lialda and Mesavant) are used clinically. However, the phenomenon of Asacol and similar tablets passing through the gut intact has been described (Sinha et al., 2003; Safdi, 2005; Ibekwe et al., 2006b, 2008). Interestingly, we recently reported the same phenomenon with Eudragit S-coated pellets (McConnell et al., 2008c). The failure to disintegrate may be due to the target pH not being reached in some subjects, or not being high enough for a long enough time for the pH-responsive film coating to dissolve, and this was the subject of an in vivo study on the matter (Ibekwe et al., 2008). This study served to confirm the complexity of such systems; these are not single trigger systems. These are a multitude of other physiological parameters affecting this, such as the fluid composition and volume described previously, transit time and retention time at the appropriate pH. Obviously, better understanding of these physiological factors is important, but also examining how they interact with each other is essential.

Dosage form factors are also influential in these pH-responsive systems, and movement away from single unit systems may be beneficial. Lamprecht and co-workers have shown interesting and promising results in rats using nanoparticles to treat inflammatory bowel disease (Lamprecht et al., 2005). Nanoparticles in particular appear to accumulate in the inflamed tissue. However, despite extensive research on novel methods of oral drug delivery (polymeric microparticles and nanoparticles, liposomes, self-micro-emulsifying drug-delivery systems, solid–liquid nanoparticles) the industry remains conservative, with tablets, capsules and pellets being the only viable investments. Unless the aforementioned new technologies show improved transit, bioavailability or some other demonstrable advantage over conventional dosage forms, and have easy scale-up and are financially viable, they may not be adopted by the pharmaceutical industry. Concerted efforts towards this should be made in research, as well as proof-of-concept, since the final goal in this field is better treatments for the patients.

An example of a new technology for colonic delivery is the MMX system (Cosmo Pharmaceuticals, Spain), used in Lialda (USA) and Mesavant (Europe) which contain high dose mesalazine for inflammatory bowel disease (Kamm et al., 2007). This comprises a hydrophilic/lipophilic matrix core with a gastro-resistant, pH-dependent coating. Once the coating dissolves and fluid imbibles into the core; a viscous gel mass forms through which the drug diffuses out. This allows once daily dosing for ulcerative colitis, a chronic condition which can sometimes require several “regular” tablets in divided doses. This is novel, but still incorporates a pH-responsive mechanism and potentially subject to the same flaws as its predecessors. Another new product for the treatment of active ulcerative colitis is Clipper® (Chiesi Farmaceutici S.p.A., Italy). This is an oral controlled release preparation of beclometasone diproponate which has a methacrylate film coating (Eudragit L100/55) and a hydroxypropyl methycellulose core (Rizzello et al., 2002).

5. Helping or hindering? The gastrointestinal microflora

5.1. Drug delivery utilising intestinal bacteria

Bacteria are ubiquitous along the gastrointestinal tract, although some areas are more heavily colonised than others (Table 1). The bacterial concentration in the stomach and proximal small bowel is modest when compared to bacterial concentrations further along in the gastrointestinal tract (Simon and Gorbach, 1984). This makes the high bacterial concentration in the colon a unique feature and one which influences the luminal environment and drug and dosage form behaviour. There are over 100 billion bacteria in the gut and 400 different species (Eckburg et al., 2005) which ferment undigested material, are metabolically active and affect the redox potential and pH of the lower gut. The difference between bacterial concentrations in the upper and lower gut (Table 1) can be exploited in order to initiate site-specific drug release in the colon (Basit, 2005). Pro-drugs, for example sulfasalazine, which rely on the action of colonic bacteria to break down an inactive precursor and release the active drug moiety, have been in use for many
conditions in which transit time is altered, such as irritable bowel syndrome or diet or disease. In particular, microflora can be affected by the use of antibiotic and/or probiotic therapies. Highly concentrated probiotics with 450 billion live freeze-dried bacteria (VSL#3®) have been produced by Actia Farmaceutica Ltda, Italy. A pilot study was carried out with this probiotic cocktail investigating its potential for the maintenance of remission in patients intolerant to aminosalicylates (Venturi et al., 1999). The duration of the study was 12 months and 15 out of the 20 patients remained in remission from ulcerative colitis over this period. However, if probiotics are to be routinely used in patients with ulcerative colitis the implications need to be considered. Probiotics produce short chain fatty acids which reduce the luminal pH of the large intestine (Gionchetti et al., 2007). This will certainly influence the performance of pH-responsive dosage forms.

5. The effect of the microflora on drug metabolism

Microbially triggered drug release is an example of how we can exploit the gastrointestinal conditions to manipulate drug release, and very successfully in the case of amyllose (COLAL™). However, there are other considerations. One hundred billion metabolically active bacteria have potentially serious implications for drug stability. In fact, it has been suggested that gastrointestinal microflora has the ability to act as an organ with a metabolic potential equal to or greater than that of the liver (Scheline, 1973). To date, more than 30 drugs have been identified as substrates for intestinal bacteria (reviewed by Sousa et al., 2008) and these include omeprazole (Watanabe et al., 1995), digoxin (Lindembaum et al., 1981), ranitidine (Basit and Lacey, 2001), nizatidine (Basit et al., 2002a) and nitrazepam (Takano and Sakai, 1990). As mentioned previously, the number of drugs reaching the colon is expected to increase, with the continuing use and development of modified release drug delivery systems and the introduction of new poorly soluble drug candidates. This means they are potential substrates for the colonic microflora. There are three potential pharmacological outcomes of bacterial metabolism of a drug: inactivity, activity, or toxicity. A significant, and worrying, example of this latter was the use of sorivudine in Japan in 1993. This drug was transformed by gut flora into (E)-5-(2-bromovinyl)uracil which can become highly toxic in the presence of 5-fluourouracil. Within 40 days of reaching the Japanese market, sorivudine was responsible for the death of eighteen patients that were co-administered sorivudine with oral 5-fluourouracil pro-drugs (Okuda et al., 1998). Sorivudine was withdrawn from the market soon after these deaths. This highlights not only the importance of understanding the potential for bacterial metabolism of drugs but also the need for careful clinical trials.
only the importance of studying bacterial metabolism of drugs, but also their effect on drug interactions.

6. Mucosal considerations

6.1. Enzymes and transporters

Before drug permeations can occur at the epithelial surface, several barriers need to be surmounted. The mucus layer can hinder drug diffusion, and its thickness and turnover rates vary along the length of the gastrointestinal tract (reviewed by Varum et al., 2008). After this is the unstirred water layer which is thought to be around 40 μm in thickness (Levitt et al., 1990). Upon reaching the epithelial layer, absorption can depend upon the route of ingress and by cellular mechanisms (influx and efflux transporters, metabolic enzymes). The transcellular pathway involves the movement of ions across the cytoplasm via channels and carriers. The paracellular pathway involves movement through intercellular spaces, and is controlled by tight junctions. There are more restrictive tight junctions in the colon rendering drug absorption more difficult via this route. In celiac disease there is an increase in intestinal permeability (Thomson et al., 2001) due to a “loosening” of tight junctions (Schulzke et al., 1998) and investigations are being carried out into making the intestine more “leaky” by using absorption enhancers to open tight junctions (Whitehead et al., 2007). These studies often use cell cultures and there is particular interest in using the approach to facilitate the absorption of oral insulin. The recent withdrawal of ExuberaTM (inhaled insulin) from the market due to poor uptake and compliance by patients demonstrates a lack of confidence in inhaled products for this purpose. This should renew interest in the oral route for protein delivery, and perhaps oral, modified release products will have more success.

There is considerable interest in the roles of efflux transporters such as P-glycoprotein (P-gp), which expels drug substrates back into the lumen, influx transporters which can enhance absorption, and in cytochrome P450 (CYP) enzymes which are responsible for drug metabolism: drug bioavailability and pharmacokinetics can be significantly affected by these (Petri et al., 2006), and levels are influenced by site, and by disease. For example, CYP levels are generally higher in the small intestine than in the colon (Bieche et al., 2007) but they are less well studied in the colon (Berggren et al., 2007). There is conflicting evidence as to the varying P-gp levels in the small intestine and the colon but new studies suggest that the levels are around 4.5 times higher in the small intestine (Berggren et al., 2007). There are a whole host of other transporters but studies on their levels along the small and large intestines are sparse (Englund et al., 2006; Meier et al., 2007; Ford et al., 2003). There is mixed evidence on the influence of disease, for example changes have been reported in transporter and enzyme levels with inflammation, cancer or cholera (Bergheim et al., 2005a; Camilleri et al., 2007; Englund et al., 2006; Meier et al., 2007; Canaparó et al., 2007; Flach et al., 2007; Wallaert et al., 1992; Linskens et al., 2001). The levels of transporters and metabolising enzymes also vary within subpopulations and the presence of polymorphisms affects the bioavailability and toxicity of a drug. In fact, the FDA is now encouraging voluntary submission of pharmacogenomic data with new drug applications (FDA, 2008).

The colon, often considered a poor site for drug absorption, may prove to be an excellent site for some drugs. A recently published study used simvastatin (a substrate for CYP3A) delivered by immediate release and delayed release dosage forms, the latter to bypass the upper small intestine and benefit from the lower levels of CYP3A in the ileum and colon. This approach increased the bioavailability by a factor of three (Tubic-Grozdanis et al., 2008), highlighting an important reason to expand research into site-specific colonic delivery away from just inflammatory bowel disease treatment. There are several drugs which have been reported to have good absorption in the colon, and these include theophylline (Staib et al., 1986), metoprolol (Godbillion et al., 1985), niefidipine (Bode et al., 1996) and ibuprofen (Wilson et al., 1989). There is expected to be an increase in the numbers of drugs which are shown to have good absorption in the colon.

The effect of transporters on bioavailability brings up the concept of “active excipients”. Excipients have been generally considered to be inert. However, in addition to the transit effects described earlier, several excipients have now been shown to have an effect on cellular transporters. For example P-gp and breast cancer resistance protein (BCRP) are inhibited by PEG-300, Pluronic P85, Cremophor EL, Tween 20, Span 20, Pluronic P85 and Brij 30 (Johnson et al., 2002; Yamagata et al., 2007a,b). P-gp is also known to be inhibited by α-tocopherol polyethylene glycol 1000 succinate, Tween 80, PEG 400 and chitosan–4-thiobutylamidamide. Gender differences in expression of BCRP and P-gp have been described (Schuetz et al., 1995; Merino et al., 2005; Zamber et al., 2003), and so the effect of excipients may be variable by gender. This was seen in a new study, in which PEG 400 enhanced the bioavailability of ranitidine in men, but not in women (Ashiru et al., in press). This may be due to differences on the effect of PEG400 on cellular transporter mechanisms between the sexes.

The area of active excipients has been reviewed recently by Buggins et al. (2007), in which they look at the effects of cosolvents, surfactants and cyclodextrins on absorption, metabolism and excretion. This raises the question, how many other so-called inactive ingredients are having an active effect on transporters, enzymes and ultimately on drug absorption?

6.2. Drugs or vaccines for lymphatic delivery

The small intestine and colon are lymphatic organs. Peyer’s patches in the small intestine and lymphoid follicles in the colon can take up antigenic and particulate material, and pathogens. This route could be exploited for drug or vaccine delivery.

There are two major clinical targets for lymphatic targeting: HIV and cancer (O’Driscoll, 2003). For example, Griffin and O’Driscoll (2006) used lipid-based formulations to achieve lymphatic transport of saquinavir (an antiviral medication) in rats. Drugs administered by this route can avoid first-pass metabolism but the major difficulties faced with this route are the low bioavailability, and poor reproducibility of uptake. In addition to Peyer’s patches and follicles, there are intra-epithelial lymphocytes which increase in number in response to infection and in celiac disease (Shiner et al., 1998). The delivery vehicle here is important; lipophilic drugs in oil bases have more opportunity to be absorbed this way, and liposomes have potential applications. The uptake of nanoparticles by cells lining the gastrointestinal tract is now a well-researched phenomenon; however, whether this uptake is significant enough to render a therapeutic effect is still under debate (Florence, 2005).

Vaccination is less dose-dependent than drug delivery. Although oral vaccination is being researched extensively, the colon has been neglected. Rectal vaccination cannot target the whole colon, but an abundance of lymphoid tissue and a lower proteolytic activity than the upper gut, suggest that oral site-specific colonic vaccination could be feasible. The immunological environment in the colon is also much less studied, and may have potentially different applications to other vaccine routes. For example, connections with the female genital tract (Kutteh et al., 1988; Kutteh, 2001), differences to small intestinal and rectal delivery (McConnell et al., 2008a) and preferential induction of immune response to bacterial antigens,
e.g. cholera or salmonella (Elson, 2001) might suggest the potential for vaccination against enteric bacteria, sexually - and vertically - transmitted diseases and colorectal tumours. This is an intriguing new avenue for the colon, if it were explored more thoroughly.

7. In vitro guides, in vivo decides: modelling the intestine

Given our discussion on the limited fluid volume, and the complex gastrointestinal fluid, it comes as no surprise that in vivo behaviour cannot easily be predicted from commonly used in vitro testing methods. Standard in vitro testing is carried out in 900–1000 ml of acid or buffer solution (USP I-II dissolution tests). Under these conditions, for example, enteric-coated products designed to release in the small intestine dissolve very rapidly in vitro in simulated small intestinal conditions (Catteau et al., 1994), but take over 2 h to dissolve in vivo in the human small intestine (Catteau et al., 1994).

Other USP dissolution tests use smaller volumes than USP I-II and are subject to different mechanical forces, but how reflective these are of in vivo situations is questionable. There is, as yet, no ideal method for modelling intestinal fluids, and fluid composition and volume aside, fluid dynamics, motility and transit are also influential.

The Institute of Food Research (Norwich, UK) have developed a state of the art model gut, which simulates gastric digestion. It is based on current biochemical and mechanical knowledge from the in situ stomach, including motility and shear (Rich et al., 2002). It incorporates inhomoogeneous mixing behaviour with more realistic emptying into a model duodenum. Currently it is used for the in vitro digestion of foods (Chambers et al., 2004; Mandalari et al., 2008; Moreno et al., 2005). The TNO intestinal model (TIM) (TNO Pharma, Netherlands) is a computer-controlled model that simulates in vivo fluids at more realistic volumes, with more realistic fluid dynamics relative to the human stomach and small intestine. This also incorporates enzymatic activity, bile salts and pancreatic juices (Minekus and Havenaar, 1996).

A follow-up to the small intestinal model also combines a simulated colonic environment (TIM2, TNO Pharma, Netherlands). However, since the large intestine especially is so poorly characterised it is difficult to model accurately. As the colon becomes more important, in light of modified release dosage forms, we will start to realise that information on the colonic environment is essential. Systems used to model the colon for metabolic or nutrition purposes (reviewed by Sousa et al., 2008) include: static batch cultures which are suitable for short time periods (<24 h) and have been used for drug delivery (Basit et al., 2004); semi-continuous systems which have the addition of nutrients at defined intervals (Rumney and Rowland, 1992); or the continuous culture system which models a dynamic equilibrium by continuously adding growth media and removing spent culture (MacFarlane et al., 1998) as well as controlling pH, redox potential and temperature. The use of bacterially based dissolution tests for dosage forms has been reviewed by Yang (2008).

In terms of drug delivery research, such intestinal modelling systems are still at an early stage, and are far from becoming a routine method of testing; they have a very low throughput, and are costly. The question arises: is it possible to fully characterise and model the ever changing intestinal milieu?

The models described above are useful only for dosage form disintegration and dissolution, and do not consider the absorption of the drug through the luminal surface. Researchers are using cell culture models to mimic the gut, for example Caco-2 cell cultures (Lentz et al., 2000). Artursson and co-workers have incorporated follicle-associated epithelium into this in vitro model, and used this to study nanoparticle uptake (Rieux et al., 2005). A continuous dissolution/Caco-2 system was developed from dissolution apparatus and a diffusion cell, such that drug dissolution and permeation across a Caco-2 monolayer would occur sequentially and simultaneously (Ginski et al., 1999). This system generally matched observed dissolution–absorption relationships from clinical studies. For example, the system predicted successfully that modified release formulations of metoprolol and ranitidine were permeation-rate-limited. Another modified release formulation (piroxicam) was predicted to be dissolution rate limited, and an immediate release piroxicam formulation was predicted to be permeation rate limited.

Whether in vitro dissolution tests, or in vitro absorption studies, more in vivo information is required to improve these methodologies. There are a plethora of techniques which can be adopted and utilised to improve our knowledge of gastrointestinal physiology.

8. Why model when you can measure?

Fundamental knowledge on the gastrointestinal environment can be obtained using invasive techniques, such as obtaining aspirates of intestinal contents, and several research groups are using this approach to further our knowledge on luminal gastrointestinal conditions (Kalantz et al., 2006a; Perez de la Cruz Moreno et al., 2006; Persson et al., 2005; Lindahl et al., 1997). Non-invasive techniques can also be employed. The pH in the human studies described previously (Evans et al., 1988; Fallingborg et al., 1989; Ilebekwe et al., 2008) was measured in situ using pH-sensitive radiotelemetry. Radiotelemetric devices, such as the Bravo® pH capsule, are pH-sensitive devices comprising of pH electrodes and radio frequency transmitters encased in an ingestible capsule body and are normally used to measure the pH in patients for diagnostic purposes. Other examples of the pH-sensitive technologies used for diagnosis are the Heidelberg pH capsule, and the remote control pH-sensitive radiocapsule (Colson et al., 1981; Remote Control Systems, London). SmartpH® is a wireless pH and pressure recording capsule that has so far been utilised in studying GI transit, motor activity and gastric contractions for disease diagnosis (Hasler et al., 2007; Reddymasu et al., 2007). New “camera in a capsule” technology (Given Imaging Olympus and Intromedic) has allowed the exploration of the small intestine which was previously very difficult to image (Kurella et al., 2007; Thomson et al., 2007; Galmiche et al., 2008). The most recently developed capsule endoscope is MiroCam® developed by MicroMedic, Korea. This relies on low frequency electric currents for the transmission of signals from the camera to the sensor pads placed externally on the body. It has a field of view of 150° and a battery life of 11 h (Intromedic, 2008). Engineered devices (InteliSite® and Enterion®) have been developed that allow the assessment of drug bioavailability from different regions of the gastrointestinal tract (Parr et al., 1999; Hinderling et al., 2007). These are remotely activated and radiolabelled (Wilding, 2000). Technologies such as this, along with gamma scintigraphy, magnetic resonance imaging and magnetic marker monitoring, are now at our disposal and should be utilised to improve our fundamental understanding of physiology and relate the results to drug delivery.

9. Concluding remarks

There is no such thing as an average person. In every person physiology is variable, from gut contents to cellular mechanisms. To move forward successfully in oral drug delivery this must be acknowledged. Furthermore, to know where we are going in the future, we must appreciate where we have been in the past. The
study of the gastrointestinal tract is an evolving field, with new enzymes and transporters being discovered at what seems an exponential rate. There are many exciting new avenues in drug targeting, and intestinal delivery, but we must not forget the basics. There are still gaps in our knowledge, and efforts must be made to fill in the missing pieces of the puzzle.

Acknowledgments

The authors would like to acknowledge the help of the members of the Basit Research Group for their helpful comments and suggestions: particular thanks goes to Dr. Fang Liu and Mr. Hamid Merchant.

References
