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Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery

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Abstract

The authors firstly review the literature dealing with drug absorption sites in the gastrointestinal tract. Descriptions are given of the methods used in determining the location of these sites, and the advantages and disavantages of each method are critically discussed. The results obtained concerning the absorption sites of the drugs used in the in vivo methods studied are given in a tabular form and several factors influencing drug absorption are briefly reported. Mechanisms of drug absorption in the human body and their influence on absorption sites are examined. Finally, there is a discussion of various dosage forms which are used for targetting drug absorption to specific sites.

Keywords: Gastrointestinal tract; Absorption site; Absorption mechanisms; Site-specific delivery; Dosage forms; Absorption window

1. Introduction

The principal goal of oral controlled-release delivery systems is to deliver the drug in a time frame that will increase efficacy and minimize adverse effects (Robinson and Mauger, 1991). The device has to control or limit the entry of the drug into the blood stream (Davis, 1987). This is achieved with conventional dosage forms containing drugs that are easily absorbed throughout the entire gastrointestinal tract. However, some drugs tend to be absorbed in specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding of the drug to the gut contents, as well as to the degradation of the drug by microorganisms present in the colon (Fuhr et al., 1992; Sinko et al., 1994; Davis et al., 1986a). The delivery site has to be controlled in order to control the absorption.

Physiological factors such as gastrointestinal transit time, regional pH, surface area, enzymatic activity and colonic microflora influence drug absorption; some of these factors may be used to achieve control over drug absorption (Dressman et al., 1993). Thus, drugs may be delivered at a specific region in the gastrointestinal tract, the so-called absorption window, by increasing the gastric residence time of the dosage form, by preventing the drug from being released before

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reaching the desired absorption site by using a protective coating and by using the microbial enzymes in the large bowel to cleave specific bonds.

Little is known about local absorption characteristics along the gastrointestinal tract for most drugs (Brockmeier et al., 1985). The present article provides an update on the drugs which have been investigated. After a description of the methods used for determining the absorption sites of drugs, the different absorption mechanisms are rewieved in relation with their absorption site. Then, various dosage forms will be discussed according to the preferential absorption sites of the drugs administered. It should be noted that the concept of mass transport models will not be developed here (Amidon et al., 1980; Komiya et al., 1980). Furthermore, the gastrointestinal transit time as well as the various factors influencing the transit, related to the subject and to the dosage form, have been recently thoroughly reviewed by Follonier and Doelker (1992) and will not be reported here.

2. Determination of the absorption site of drugs

The absorption site of a drug along the gastrointestinal tract may be investigated either by in situ or by in vivo methods.

2.1. In situ methods

These methods include open loop techniques such as single-pass perfusion, recirculating perfusion and oscillating perfusion as well as closed-loop techniques (Schurgers et al., 1986; Kararli, 1989).

A drug solution is placed or perfused in a predetermined gastrointestinal site of an animal model (rat, dog, monkey or rabbit). The perfusion rate varies according to the method used. According to Schurgers et al. (1986), perfusate hydrodynamics should be defined in detail and kept constant throughout the experiment since they may have an influence on the aqueous boundary layer and therefore on the absorption rate of a drug.

The amount of drug or metabolite is measured either in the blood stream (portal vein, peripheral blood) or in the loop. There is an appreciable membrane storage in the case of highly lipophilic drugs during gastrointestinal absorption which may destroy the direct correlation between drug absorption and luminal disapearance (Doluisio et al., 1970; Taylor et al., 1981; Nook et al., 1988). Furthermore, in order to measure in the loop, a non absorbable marker such as PEG 4000, phenol red or inulin, is often added to the drug solution to assess the net intestinal water transport (Doluisio et al., 1969; Sinko et al., 1994). However, Gabus-Sannié and Buri (1987) have shown that these tracers are partially absorbed or adsorbed.

The following information about the absorption of a drug has been obtained by in situ methods:

(1) — the absorption sites of a drug according to drug permeability differences throughout the gastrointestinal tract; a dimensionless wall permeability (P_w^*) may be calculated for each site investigated (Langguth et al., 1994; Yee and Amidon, 1990). However, the number of animals used has to be sufficiently high to demonstrate the permeability differences from a site to another; because of animal to animal variability it is difficult to obtain multiple permeability measurements in the same experimental animal (Lu et al., 1992);

(2) — the influence of the pH on the extent of drug absorption (Brennan et al., 1991; Lee et al., 1994; Oberle and Amidon, 1987; Chungi et al., 1979) as well as on the degradation of a drug (Langguth et al., 1994);

(3) — the assessment of a saturable transport mechanism (Sanchez-Pico et al., 1989), as well as the contribution of the paracellular route to the overall transport mechanism (Riad and Sawchuk, 1991);

(4) — the assessment of 'intestinal first pass effect' by quantification of any metabolites that may be produced (Davis, 1985).

A drawback of in situ methods is that they are used in isolated segments of the gastrointestinal tract which may not adequately reflect the absorption in an normal gastrointestinal tract (Kayne

Table 1
Results obtained regarding absorption sites of drugs investigated by perfusion method

Drug	Comments	Reference
1-Deamino-8-D-arginine vasopressin	Similar absorption from the stomach, duodenum and jejunum (low bioavailability). Lower absorption from the distal ileum and even lower from proximal colon.	d'Agay-Abensour et al., 1993
Griseofulvin	Strong correlation between the absorption rate and the amount of drug delivered to the test segment (proximal or distal small intestine) per unit time.	Gramatté, 1994
Levodopa[1]	No enhancement of levodopa intestinal permeability by induced net fluid absorption. Induced net fluid absorption not be responsible for the large inter- and intravariability of levodopa in Parkinson's diseases.	Nilsson et al., 1994
Metoprolol[2]	No absorption from the stomach. Amount absorbed in the duodenum and the jejunum directly proportional to the amount delivered.	Jobin et al., 1985
	Amount absorbed in the jejunum and the ileum directly proportional to the amount delivered. Lower absorption of metoprolol perfused in the jejunum in a saline solution than after gastric administration of the drug incorporated in a meal.	Vidon et al., 1985
	Similar absorption from the jejunum and the colon. Similar metabolite-to-drug AUC ratio after jejunal and colonic perfusion but higher than after i.v administration.	Godbillon et al., 1985
Nicardipine	Similar absorption from the jejunum and the ileum. Absorption slightly but significantly decreased with food (first pass metabolism in liver).	Delchier et al., 1988
Oxprenolol[2]	No absorption from the stomach. Amount absorbed in the duodenum and the jejunum directly proportional to the amount delivered.	Vidon et al., 1986
Paracetamol	Similar absorption from the duodenojejunal junction, the distal jejunum and the ileum.	Gramatté et al., 1991
Ranitidine	Double-site for drug absorption along the small intestine may explain the double-peak phenomenon in the pharmacokinetics of ranitidine (oral administration).	Gramatté et al., 1992

[1] +peripheral decarboxylase inhibitor: benserazide; [2] drug administered in an homogenized meal.

and Lee, 1993). Furthermore, animals models are different from humans with respect to the anatomy and physiology of the absorption sites (Ritschel, 1987; Kararli, 1989; Kaniwa et al., 1988). Therefore, a correlation has to be established with another method. Sutcliffe et al. (1988) compared the jejunal and ileal absorption of a range of drugs with poor to good oral absorption both in humans (intubation technique) and rats (recirculating perfusion). The authors concluded that the absorption of poorly absorbed drugs is more affected in humans than in rats by the perfusion sites and the molecular structure of the drug administered.

2.2. *In vivo methods*

In contrast to in situ methods, in vivo methods are better adapted for establishing the absorption sites of drugs but they may not allow the determination of the mechanisms of drug absorption. The absorption sites of several drugs investigated are listed in Tables 1–3 according to the method used.

Table 2
Results obtained regarding to absorption sites of drugs investigated by local instillation

Drugs	Comments	Reference
Acrivastine	Poor absorption from the colon.	Balasubramanian et al., 1989
Benazepril	Colon delivered a smaller amount at a slower rate than either small intestine or oral delivery. Metabolite-to-drug AUC ratio reduced from colon.	Chan et al., 1994
Bidisomide	Similar absorption (AUC) from the stomach, the duodenum, jejunum and the ileum. Double-peak phenomenon (stomach infusion) attributed to the more rapid drug absorption in the duodenum and ileum.	Cook et al., 1993
Captopril	Enhancement of captopril absorption in the colon from solution by controlling intestinal pH.	Brennan et al., 1991
Ciclosporine[1]	Comparable absorption (AUC) from the duodenum and the jejunum but significantly decreased from the ileum and the colon.	Drewe et al., 1992
Diclofenac Na[2]	Similar absorption from the colon and after oral administration of the drug. Lag time for oral absorption.	Gleiter et al., 1985
Digoxin	Efficient absorption from the distal part of the intestine.	Ochs et al., 1975
Gepirone	Drug absorbed throughout the entire length of the small intestine. No significant difference between oral administration, proximal and distal small intestine regarding to the active metabolite.	Tay et al., 1992
Glibenclamide	Similar absorption (AUC) from the stomach, duodenum and colon. Slower absorption rate from colon than from upper gastointestinal tract.	Brockmeier et al., 1985
Levodopa	Similar absorption at any site in the upper small intestine after pretreatment and co-administration of a peripheral decarboxylase inhibitor (benserazide).	Gundert-Remy et al., 1983
Octreotide (synthetic somatostatin analogue)	Comparable absorption from the stomach, duodenum, jejunum and ileum but tendency to decreased peptide absorption after duodenal and ileal administration. Considerable variation both inter- and intra-subject.	Köhler et al., 1987
Piretanide	Similar absorption from the stomach and the duodenum. Slower and incomplete absorption from the colon. Gastric absorption after immobilization of the stomach. Considerable inter-subject variation in absorption rate of piretanide from the stomach. In the stomach, the rate-limiting step seems to be dissolution. This may explain the second peak in the pharmacokinetics of piretanide (oral administration).	Brockmeier et al., 1986a; Brockmeier et al., 1986b
Pravastatin	Maximal bioavailability of pravastatin after absorption from the duodenum. Predominant conversion of pravastatin to its major metabolite in the stomach.	Triscari et al., 1993
Ranitidine	Similar absorption from the stomach and the ileum. Slower and incomplete absorption from the cecum. Double-peak phenomenon in the pharmacokinetics of ranitidine (oral administration) is not the result of variation in gastric emptying.	Williams et al., 1992

Table 2

Drugs	Comments	Reference
Sumatriptan	Similar absorption from jejunum and after oral oral adminstration of the drug. Slower and incomplete absorption from the cecum. Metabolite-to-drug AUC ratio reduced from the ileum and from the caecum.	Warner et al., 1995

AUC:[1] drug administered in an emulsion; [2] drug administered in suspension.

2.2.1. Perfusion technique

A multiluminal tube is placed in a predetermined site of the gastrointestinal tract (Fig. 1). This tube is used to introduce the drug in solution or in a homogenized meal (d'Agay-Abensour et al., 1993; Nilsson et al., 1994; Gramatté et al., 1991; Gramatté et al., 1992; Gramatté, 1994; Delchier et al., 1988; Godbillon et al., 1985; Vidon et al., 1985; Jobin et al., 1985; Vidon et al., 1986) as well as to aspirate the luminal content. It is positioned either fluoroscopically (d'Agay-Abensour et al., 1993; Nilsson et al., 1994; Vidon et al., 1985; Jobin et al., 1985; Vidon et al., 1986) or by measurement of the pH change in the aspirates of the gut content (Gramatté, 1994). The disappearance of the drug is measured in the site using non-absorbable markers. The disappearance of the drug, as for in situ methods, may be influenced by factors other than absorption, e.g. intestinal metabolism and binding to intraluminal constituents or intestinal mucosa (Vidon et al., 1985). An occlusive balloon may be used to avoid contamination by endogenous secretions and reflux of the perfusate above the infusion point (d'Agay-Abensour et al., 1993; Nilsson et al., 1994; Delchier et al., 1988; Vidon et al., 1985).

Intubation of the colon from the oral end is rarely used since aspiration of the luminal content is not considered to be feasible. The absorption may only be estimated indirectly by comparaison with i.v. administrations (Godbillon et al., 1985). Furthermore, colonic intubation can alter the anaerobic colonic environment and perturb normal physiology, as it appears to produce hypermotility (Wilding et al., 1992a; Krevsky et al., 1986).

2.2.2. Local instillation

The drug is placed via a catheter at different sites of the gastrointestinal tract which are localized by endoscopy, by fluoroscopy or by pH monitoring. Blood samples are then collected at various time intervals. The drug absorption is excluded from parts distal to the administration site.

The effect of the pH solution or meal may be determined in order to assess a possible degradation in the stomach as well as to assess the influence of food intake on drug absorption (Delchier et al., 1988; Vidon et al., 1989).

It should be noted that the large intestine is generally well cleansed prior to endoscopy and that the experimental situation does not correspond to normal physiological conditions (Gleiter et al., 1985). The content of the intestine is thick and may slow down the transport of some active substances to the absorption site, as was shown for indomethacin (Möller, 1989).

2.2.3. High-frequency capsule

The transit of a capsule (Fig. 2) along the gut is traced by X-ray. Once the capsule has reached the predetermined site, drug release is triggered by a high-frequency signal which induces the rupturing of a latex balloon inside the capsule (Fuhr et al., 1992). This balloon contains the drug in solution or suspension. The absorption measured could be effected by the motility and filling of the gastrointestinal tract, as it includes any absorption that takes place distally with respect to the release site (Harder et al., 1990). Furthermore, the large size of this capsule (12 mm x 28 mm) does not allow for the determination of drug absorption in

Table 3
Results obtained regarding absorption sites of drugs investigated using a HF-capsule

Drugs	Comments	References
Allopurinol[1]	Main absorption site: duodenum and upper jejunum. Slow and incomplete absorption in the lower jejunum. No saturable process in the range of doses studied.	Schuster et al., 1985
Ciprofloxacin	Main absorption site: upper part of the gastrointestinal tract (the duodenum and, to a smaller extent, the jejunum). No significant differences in absorption parameters from oral administration as a solution, as a tablet, or as a solution released in the stomach. Metabolites profile in urine independent of the absorption site. Difference in presystemic metabolism of known metabolites along the gut probably excluded.	Staib et al., 1989; Harder et al., 1990
Diltiazem	Drug absorbed throughout the gastrointestinal tract. Absorption more effective in the proximal region compared to the colon.	Rydén and Jonsson, 1989
Furosemide	Main absorption site: the upper part of the gastrointestinal tract.	Graul et al., 1985
Isosorbide-5-mononitrate	Similar absorption from the stomach, duodenum, jejunum and ascending colon.	Wildfeuer et al., 1986
Nilsodipine	Maximal absorption in the colon. First pass elimination of both parent drug and metabolites may be lower in the colon.	Staib et al., 1988a; Staib et al., 1988b
Nitrendipine	Good absorption in regions of the gastrointestinal tract.	Staib et al., 1988a
Theophylline	Complete absorption from the lower segments of the colon.	Staib et al., 1987

[1]drug administered in suspension.

the stomach, as it might be retained there until it is emptied with the interdigestive housekeeper wave.

2.2.4. *Pharmacoscintigraphy and deconvolution method*

The position of a controlled-release system within the gastrointestinal tract during the pharmacokinetic study is determined by gamma-scintigraphy (Wilding et al., 1991a). The very small amount of tracer needed has no influence on the properties of the preparation (Wilding, 1994). As opposed to methods where the drug is administered in solution, this method has the advantage of determining, under normal physiological conditions, the absorption site of a drug administered in a controlled-release dosage form as well as the effect food intake has on drug absorption (Wilding et al., 1992a). For instance, by using a single pass perfusion technique, it has been found that the length-normalized intestinal permeability for carbamazepine administred in solution was greater in the colon than in the duodenojejunum (rabbit) (Riad and Sawchuk, 1991) while carbamazepine absorption decreases when an Oros® osmotic pump is located in the human colon (Wilding et al., 1991b). This pharmacoscintigraphy study shows that the solubility of carbamazepine becomes the rate limiting factor for its absorption in the colon.

Controlled-release dosage forms are administered in the form of radiolabelled devices in which the release of the drug is independent of environmental changes such as, for example, radiolabelled osmotic devices which have a zero order release profile. For sustained-release dosage forms with first-order release profiles, the plasma concentration time curve is deconvoluted to estimate the drug remaining to be absorbed (Wilson and Washington, 1988).

A few studies deal with the absorption site by pharmacoscintigraphy. This method has confirmed the good absorption of oxprenolol throughout the entire gastrointestinal tract (Wilson and Washington, 1988; Davis et al., 1988). Fig. 3

shows the relationship between transit of an oxprenolol-loaded osmotic pump and the plasma concentration profile for 2 volunteers (Wilson and Washington, 1988). The amount of oxprenolol absorbed varies greatly depending on the colonic residence time of the device. Warrington et al. (1985) found that the absorption process of metoprolol after Oros® administration is decreased in the colon. The colonic absorption of buflomedil hydrochloride is lower than in the small intestine (Wilson et al., 1991).

It should be noted that it is possible without the use of gamma scintigraphy to study the absorption from the gastrointestinal tract of a given drug considered by a numerical deconvolution method, using an in vitro-in vivo correlation (Brockmeier, 1986). For instance, Rietbrock et al. (1992) suggest that the in vivo dissolution profile of a slow release preparation of molsidomine, revealed either a progressive decrease in dissolution velocity of the drug caused by altered physico-chemical conditions in the ileum and the colon or a progressive reduction in the absorption constant. Furthermore, a site of enhanced absorption of molsidomine in the distal colon is observed.

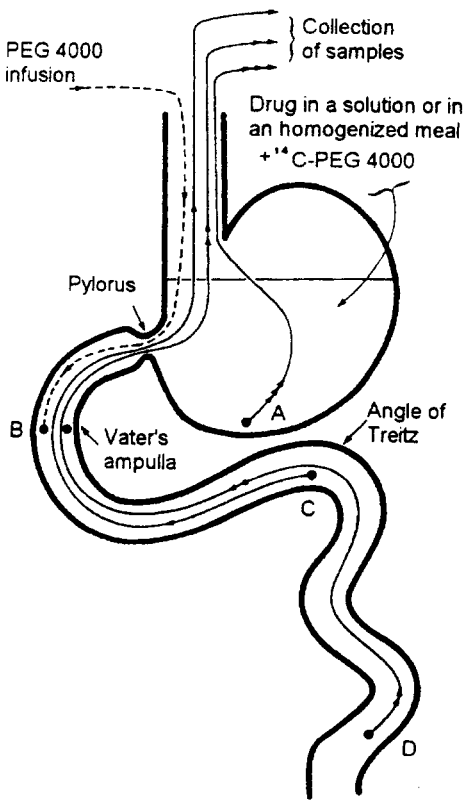

Fig. 1. Diagram of the siting of the tubes within the gastrointestinal tract for perfusion technique. Adapted from Jobin et al., 1985.

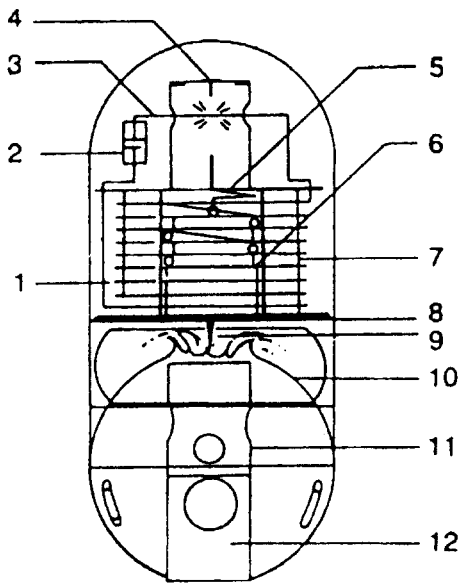

Fig. 2. Shematic diagram of the high-frequency capsule. (1) oscillating circuit; (2) capacitor; (3) heating wire; (4) nylon thread; (5) spring; (6) plunger; (7) cylinder liner; (8) separation wall; (9) small steel needle; (10) latex; (11) holder for 10; (12) plug. Reproduced from ref. (Graul et al., 1985) with permission.

3. Is there a relationship between absorption site and absorption mechanisms?

The extent of drug absorption in a segment of the gastrointestinal tract depends generally on the rate of absorption as well as on the exposed surface area and time available for drug absorption. The gastrointestinal transit times of dosage forms in the various segments of the gastrointestinal tract are listed in Table 4 along with other factors influencing drug absorption such as sur-

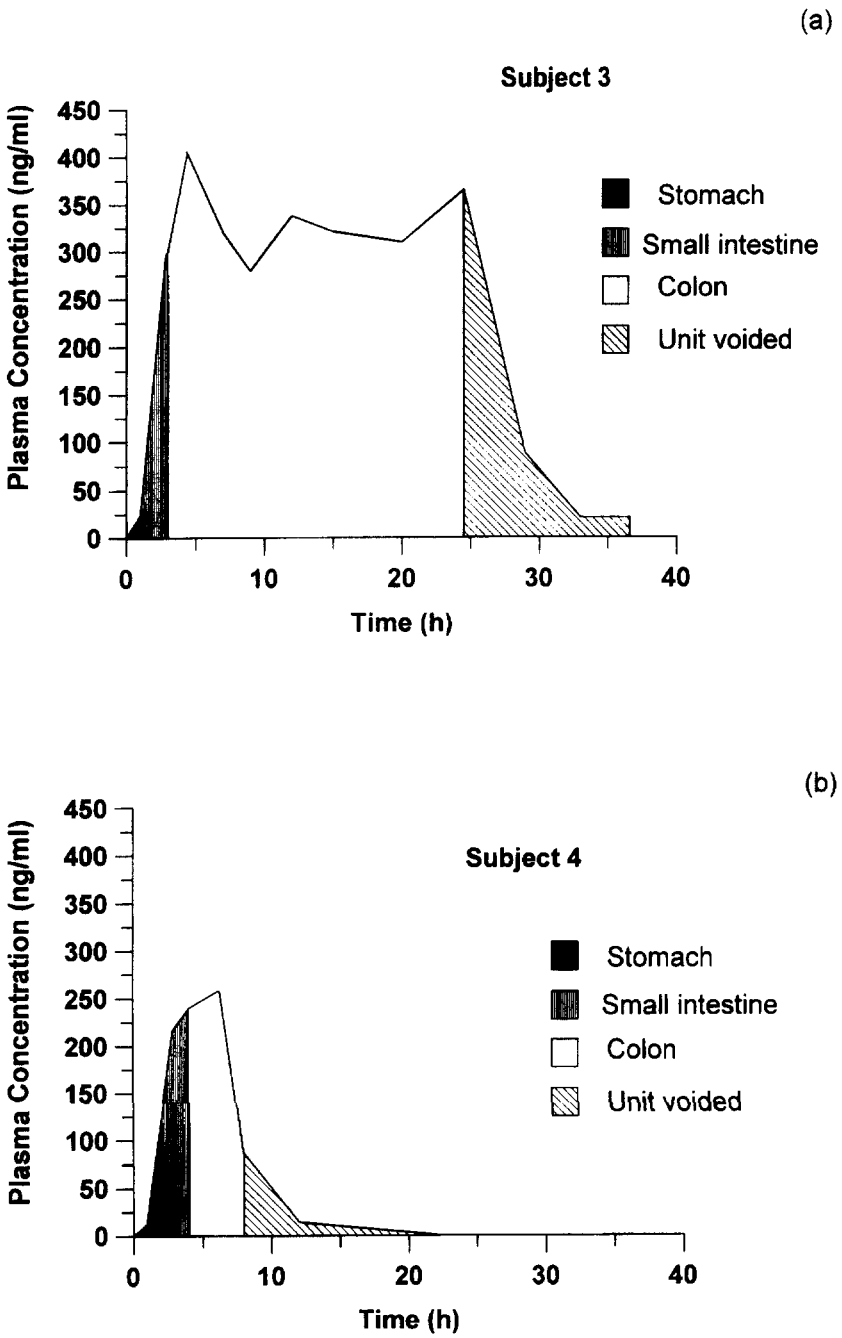

Fig. 3. Relationship between the transit of an oxprenolol-loaded osmotic pump and the plasma concentration profile for 2 volunteers. Adapted from Wilson and Washington, 1988.

Table 4
Anatomical and physiological factors influencing drug absorption and metabolism in various segments of the human gastrointestinal tract

Section	Length (m)	Absorbing surface area (m^2)	Absorption pathway[1]	Transit time (h)	pH		Enzymes and others	Microorganism (counts/g)[2]
					Fasted state	Fed state		
Stomach	0.2	0.1	P, C, A (?)	Variable	1.4–2.1	Until 6–7[3]	Pepsin, lipase, rennin, HCl	10^2
Small intestine	7	120		3 ± 1	5.5–8			
• Duodenum	0.3	0.1	P, C, A, F, I, E		5.5–6.5	4.9–6.0[4]	Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, peptidases	10^2
• Jejunum	3	60	P, C, A, F, I, E		6.1–7.1	No change	Erepsin, amylase, maltase, lactase, sucrase, peptidases	10^5
• Ileum	4	60	P, C, A, F, I, E		7–8	No change	Lipase, nuclease, nucleotidase, enterokinase, peptidases	10^7
Large intestine	1.5	0.3		1–60		No change	—	10^{11}
• Caecum		0.05	P, C, A, E		6–7			
• Colon		0.25	P, C, E		~8		—	10^{11}

[1]P, passive diffusion; C, convective transport or aqueous channel transport; A, active transport; F, facilitated transport; I, ion-pair transport; E, entero- or pinocytosis.
[2]Number of micro-organisms per gram of gastrointestinal content.
[3]Rrestoration of fasting pH after less than 2 h.
[4]Restoration of fasting pH after about 4 h.
Adapted from Faigle, 1993; Ritschel, 1991; Follonier and Doelker, 1992.

face area, absorption mechanisms, pH values, enzymes and number of microorganisms.

It should be noted that food intake increases the pH values and the gastric residence time. It is generally recognized that the main absorption site of drugs in humans is the small intestine, due to its high surface area (Davis et al., 1986a). It has been shown, however, that the colon acts as an important absorption site for some drugs such as theophylline (Yuen et al., 1993). The surface difference between the various gastrointestinal sites may only have a minor influence on the rate of absorption (Brockmeier et al., 1986b). Studying by endoscopy the absorption sites of glibenclamide administered in suspension, Brockmeier et al. (1985) show that the same amount of this drug is absorbed in the colon as in the upper part of the gastrointestinal tract, although the rate of absorption is clearly slower in the colon. As it has been already shown in Fig. 3 for oxprenolol absorption, the amount of drug absorbed in a site depends on the residence time of the drug in this gastrointestinal site. Furthermore, the small intestine is not the main site of peptide absorption in spite of its high surface area since they are largely metabolized there.

Although anatomical and physiological factors may influence strongly drug absorption, they can not explain the low permeability of some drugs.

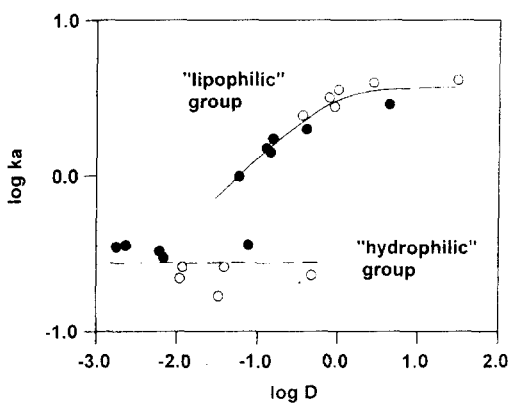

Fig. 4. Correlation between log absorption rate constant (k_a) and log distribution coefficient (D) for eleven β-blockers in the rat in situ jejunum (– • –) and ileum (– – –). Reproduced from Taylor et al., 1985 with permission.

Thus, it seems interesting to examine how the various absorption mechanisms (passive diffusion, convective transport or aqueous channel transport, active transport, facilited transport, ion-pair transport and endo- or pinocitosis (Wilson et al., 1989; Ritschel, 1991; Kararli, 1989) may influence the absorption sites of drugs.

3.1. Passive diffusion

It is thought that most drugs are absorbed by passive diffusion, controlled by the well known pH partition hypothesis (Crevoisier and Buri, 1976; Schanker, 1960; Wilson et al., 1989). The rate of passive transport depends on the solubility of the molecule in the lipid bilayer of the epithelial cells. This hypothesis assumes that acidic drugs, mostly present in their non-ionized form at low pH, are preferentially absorbed in the stomach while basic drugs are absorbed in the gut (Hirtz, 1984), as has been found, for example, for two lipophilic β-blockers, namely oxprenolol and metoprolol, which are both weakly basic drugs (pKa = 9.5 and 9.7 respectively) with an negligible absorption in the stomach (Jobin et al., 1985; Vidon et al., 1986). On the other hand, the percentage of the available drug absorbed in the duodenum or the upper jejunum is 60% for metoprolol and 80% for oxprenolol. According to Vidon et al. (1986), the differences in the absorption level of these two drugs might be related to their differing degrees of liposolubility (the partition coefficient between n-octanol and pH 7.4 buffer is 1.6 for oxprenolol and 0.5 for metoprolol) (Möller, 1989).

The limitation of the pH partition hypothesis has been well demonstrated by Taylor et al. (1985) in a study on the absorption rate of eleven β-blockers of similar pK_a values (around 9.5) in situ in the rat jejunum and ileum (Fig. 4). Similar results have been obtained by Artursson (1990), when using a human intestinal cell line (Caco-2). The plot of log absorption rate (k_a) versus log distribution coefficient (D), which is the log of partition coefficient corrected for ionization at the pH of the jejunum or ileum, has a sigmoidal shape. The pH partition hypothesis has, therefore, a predictive value only if the solubility and oc-

tanol/water partitioning remain reasonably constant or sufficiently high over the entire physiological pH range, which is rarely the case (Brockmeier et al., 1985). Furthermore, the octanol/water partitioning should not be too high.

The rate-limiting factor in the absorption of the highly lipophilic β-blockers seems to be the unstirred water layer at the surface of the intestinal epithelium (Artursson, 1990; Taylor et al., 1985). The influence of the unstirred water layer has been also reported with respect to the absorption of progesterone (a highly lipophilic steroid) in rats (Komiya et al., 1980). According to Chiou (1994), the effect of the aqueous diffusion layer is overestimated and is practically nil with respect to the extent of progesterone absorption.

3.2. Convective transport or aqueous channel transport

The absorption of hydrophilic β-blockers is also not consistent with the pH partition hypothesis (Fig. 4) (Taylor et al., 1985). Therefore, the diffusion of these drugs through the lipoidal membrane is not the principal absorption pathway. A study dealing with the absorption of carbohydrate probe molecules from rat small intestine suggests that there are at least two aqueous diffusion pathways across the intestinal mucosa, although there is no morphological evidence for this (Lee et al., 1991; Hamilton et al., 1987). Small molecules diffuse through a small channel of finite dimension compatible with a transcellular aqueous pore, whilst large molecules diffuse only through a pathway of considerably larger dimensions comparable to aqueous pores or channels across the intercellular junctional complex of the epithelium (paracellular pathway) (Hamilton et al., 1987). It has been found that the integrity of the tight junctions depends on the calcium concentration in the medium (Wilson et al., 1989; Kararli, 1989).

Various studies have attempted to correlate the molecular weight of various hydrophilic molecules with their percentages of absorption (Hamilton et al., 1987; Artursson et al., 1993; Chadwick et al., 1977). However, it appears that the permeability of these molecules is not simply inversely proportional to their molecular weight or molecular radius but depends on the molecular structure of these molecules (Hamilton et al., 1987; Artursson et al., 1993). Indeed, the permeability of PEG with a molecular weight of 194 g/mol was 6 to 28-fold higher than the permeability of mannitol (M_r, 182 g/mol) (Artursson et al., 1993). Furthermore, cations are generally more easily transported through the tight junctions than are nonionic species or anions (Rojanasakul et al., 1992; Adson et al., 1994; Hamilton et al., 1987).

The epithelial junctions become progressively tighter from the small intestine to the colon which should lead to decreased permeability to polar compounds (Chadwick et al., 1977; Mummaneni and Dressman, 1994; Rojanasakul et al., 1992). For instance, the permeability to hydrophilic β-blockers is higher in the jejunum than in the ileum (Fig. 4), and the apparent permeability coefficient of atenolol is more than five times greater in the jejunum than in the colon (in vitro) (Sasaki et al., 1994). The membrane permeabilities of the duodenum, jejunum, ileum and colon were evaluated using a combined method based on electrical conductance and on flux measurements of hydrophilic fluorescent probes (Rojanasakul et al., 1992). It has been found that the membrane permeability decreased along the intestine, although their resistance values were not statistically different. The paracellular route is suggested to be responsible for absorption in the upper gastrointestinal tract of drugs such as hydrochlorothiazide (Taylor et al., 1989), small peptides (Bohner et al., 1995; Rojanasakul et al., 1992; Adson et al., 1994) and nucleoside analogue such as didanosine (Sinko et al., 1994) and 3'-azido-3'-deoxythimidine (AZT) (Park and Mitra, 1992).

Paracellular diffusion of a drug does not, however, exclude other mechanisms of absorption. For instance, according to Gan et al. (1993), ranitidine is transported predominantly via paracellular pathways and is absorbed mainly by the small intestine (Williams et al., 1992). Yet, by the perfusion of ranitine in various sites of the small intestine, it was found that the small intestine has a middle region of diminished absorption which has not yet been explained (Gramatté et al., 1992). Mummaneni and Dressman (1994) confirmed this fact by using an in vitro everted ring

Table 5
Drawbacks of several gastroretentive dosage forms

Formulation	Drawbacks
Passage-delaying excipients or agents (Gröning and Heun, 1989; Li et al., 1987)	Affect the emptying mechanisms of the entire stomach content.
Biodegradable and non biodegradable formulation which the size or shape retain the dosage form in the stomach (Cargill et al., 1988; Shalaby et al., 1992; Banker, 1973)	Present the hazard of permanent retention and might lead to serious life threatening effects if multiple dosing is prescribed.
Bioadhesive drug delivery systems (Longer et al., 1985; Harris et al., 1990a)	Adhesion is nonspecific, since they can adhere to the oesophagus mucosa. Efficiency limited by the turnover time of the intestinal mucus gel layer and by the possible interaction with food (Lehr et al., 1992). The gastrointestinal transit time did not appear to be greatly affected by the adhesive or control materials included (Harris et al., 1990b; Khosla and Davis, 1987).

technique and reported that transcellular absorption may also be an important route of absorption, since colonic uptake of ranitidine was only 70–80% of the jejunal uptake.

3.3. Facilited and active transport

Some drugs, such as furosemide (Chungi et al., 1979; Ritschel et al., 1991; Graul et al., 1985), *p*-aminobenzoic acid (Yasuhara et al., 1983) and riboflavin (Levy and Jusko, 1966), principally absorbed by saturable mechanisms, have an absorption site in the upper gastrointestinal tract as there is no carrier identified in the lower bowel (Sanchez-Pico et al., 1989). It is presumed that piretanide, a drug which has structural and physico-chemical similarities to furosemide (Merkle et al., 1976), is also absorbed by a saturable mechanism since its absorption is not consistent with the pH partition hypothesis and since it shows a low absorption from the large intestine (Brockmeier et al., 1986b).

It has been found that levodopa shares the same transport mechanism as the absorption of large neutral amino acids across the jejunal mucosa (Nilsson et al., 1994). A peptide transport system in the small intestine, distinct from the amino acid transport carriers (Friedman and Amidon, 1990), is responsible for the uptake of oligopeptides and some peptide-like therapeutic agents (Kim et al., 1994), β-lactam antibiotics (Sanchez-Pico et al., 1989; Hildago et al., 1995), octreoctide (Fricker et al., 1992) and ACE inhibitors (Friedman and Amidon, 1989; Friedman and Amidon, 1990; Grass and Morehead, 1989; Yee and Amidon, 1990; Kim et al., 1994). It appears that the β-lactam antibiotics show consistently high capacity and low affinity to the transporter in contrast to ACE inhibitors (Friedman and Amidon, 1990). The absorption of peptide drugs is highly decreased in the colon although passive transport of these compounds may occur simultaneously with the saturable transport.

3.4. Ion-pair transport

The absorption of quaternary ammonium derivatives, strong sulfonic acids, carbenoxolone and tetracycline are not consistent with the pH partition hypothesis (Schanker, 1960; Fiese and Perrin, 1969; Perrin and Vallner, 1970; Crevoisier and Buri, 1976). It is assumed that they are absorbed by ion-pair transport. However according to Blanchard et al. (1990), a more likely explanation for carbenoxolone absorption is that at low pH values, some carbenoxolone precipited out of the solution during the perfusion experiments, thereby reducing the driving force for diffusion across the intestinal wall.

3.5. Pinocytosis

Pinocytosis is not a significant transport mechanism. However, a small amount of large-sized molecules such as peptides, proteins and particles are absorbed by endocytosis or pinocytosis in the enterocytes and the Peyer's patches regions (Eldridge et al., 1991; Kararli, 1989; Wilson et al., 1989). However, in enterocytes, macromolecules are extensively degraded (Ho et al., 1990). Furthermore, the local immunological response exerted by the gut-associated lymphoid tissues constitutes an obstacle to the absorption of large peptides (Kararli, 1989). Peyer's patches are located primarily in the ileum of humans and allow the transport of macromolecules to the lymphatic system (Ho et al., 1990). Therefore, the gastrointestinal absorption of these molecules is low and should be site-specific, i.e. consistent with the Peyer Patches location. This route of absorption seems to be promising for oral administration of macromolecules extensively destroyed in the gut. For instance, biodegradable microspheres (1–10 μm) when used as a delivery system for vaccines are adsorbed, in mice, into the Peyer's patches and their draining lymphatics (Eldridge et al., 1991). However, it is not possible to extrapolate this results to humans since the distribution, size and number of Peyer's patches in the small intestine vary among the species (Ho et al., 1990). Furthermore, this site may not be a good target site beyond mid-age since Peyer's patches drastically decrease with increasing age (Ritschel, 1991).

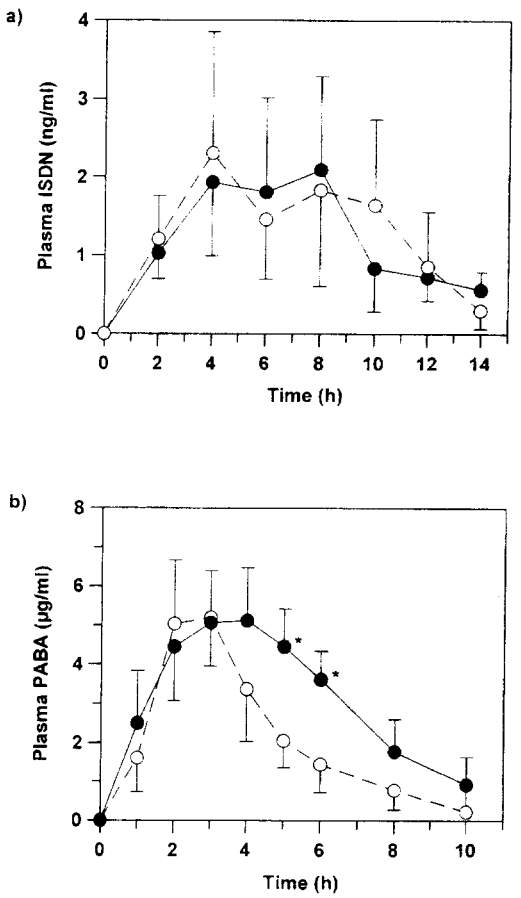

Fig. 5. Plasma levels after administration of pills to beagle dogs: (– • –) floating pills; (– ◦ –) control pills; Mean (S.D.) ($n = 6$); (*) $P < 0.05$ (significantly different). (a) isosorbide dinitrate (ISDN); (b) *p*-aminobenzoic acid (PABA). Reproduced from Ichikawa et al., 1991a with permission.

4. Dosage form targeting in the gastrointestinal tract

By using adapted formulations, it is possible to target three different parts of the gastrointestinal tract, namely the stomach, the small intestine and the colon.

4.1. Prolonging the gastric residence time of dosage forms

The transit time of a dosage form through the gastrointestinal tract is variable, or even unpredictable, and can be of very short duration (Table 4). Thus, the time available for the drug absorption might be limited. This is of great importance for drugs for which absorption is limited to certain sites along the gastrointestinal tract. More specifically, it is important for controlled-release dosage forms. Therefore, it appears useful to increase the gastric residence time for drugs predominantly absorbed in the upper gastrointestinal tract or for drugs that are practically insoluble in the intestinal fluid such as diazepam, chlordiazepoxide and cinnarizine (Machida et al., 1989; Sheth and Tossounian, 1984; Müller-Lissner et al., 1981).

The different approaches proposed to prolong the residence time of delivery systems in the stomach have been reviewed in detail by Moës (1993) and Timmermans (1991). It appears that there are various approaches, some of which have drawbacks which could limit their uses. They are summarized in Table 5.

More promising approaches for prolonging the residence time of delivery systems in the stomach are based on the density of the dosage form (heavy pellets and floating dosage forms), although the efficiency of these dosage forms is controversial (Follonier and Doelker, 1992).

The formulation of high density pellets is based on the assumption that heavy pellets might remain longer in the stomach, since they are positioned in the lower part of the antrum (Moës, 1993). Devereux et al. (1990) reported that an increase in density from 1.5 to 2.8 g cm^{-3} significantly delayed the time for 50% of the 1 mm pellets tested to empty from the stomach ($t_{50\%}$) in both the fasted and the fed state. The gastric emptying time was prolonged in the fed state. Moreover, Clarke et al. (1993), using the same experimental procedures (fed state), found that the gastric emptying rate was significantly different for pellets (0.5 mm) with densities of 1.5–2.6 g cm^{-3}. However, in investigations on the gastric emptying of larger pellets (4.75 mm) with similar densities (1.5–2.6 g cm^{-3}), Clarke et al. noted that the increase of gastric retention for large pellets was not significant. The author ascribed this result to the variability in the emptying times of large pellets, which precluded the detection of any real differences. In another study, Clarke et al. (1995) concluded that the critical density to achieve prolonged gastric residence lies between 2.4 and 2.8 g cm^{-3}, since no prolongation or delay was observed between pellets of 1.5, 2.0 and 2.4 g cm^{-3} with a diameter of 1.2–1.4 mm. To our knowledge, until now, heavy pellets have never been used to increase the gastric residence time of drugs predominantly absorbed in the human upper gastrointestinal tract. In veterinary medicine, Evrard (1995) have shown that heavy matrix bolus of density greater than 2.0 can be retained in a special part of the bovine stomach, namely the reticulo-rumen. This dosage form prevents the regurgitation as well the gastric emptying to the intestine.

Various floating dosage forms are proposed for achieving intragastric retention (Timmermans and Moës, 1990; Timmermans, 1991; Moës, 1993). Capsules such as hydrodynamically balanced systems (HBS), tablets or granules containing a swellable hydrocolloid in which air trapped by a swollen polymer brings about their buoyancy (Miyazaki et al., 1988; Menon et al., 1994; Sheth and Tossounian, 1979; Erni et al., 1983; Sheth and Tossounian, 1984; Müller-Lissner et al., 1981). Gas-generating systems may be incorporated into the dosage form in order to increase the buoyancy (Ushimaru et al., 1985; Machida et al., 1989; Hilton and Deasy, 1992). However, the optimization of the drug release may alter the buoyancy. Thus, it is sometimes necessary to separate the control of the buoyancy and that of the drug release kinetics. Several dosage forms are based on this principle: bilayer capsules or tablets (Inouye et al., 1988; Oth et al., 1992; Ingani et al., 1987); pills surrounded by two layers (one effervescent and one swellable) (Ichikawa et al., 1991b); laminated film-type preparations (Machida et al., 1989); and hollow granules or microspheres (Kawashima et al., 1991; Thanoo et al., 1993; Inouye et al., 1989). It should be noted that other devices which are only described in a patent (Michaels, 1974; Michaels et al., 1975; Harrigan, 1977) will not be discussed here because they are too sophisticated for commercial use.

Various authors (Sangekar et al., 1987; Müller-Lissner and Blum, 1981; Davis et al., 1986b) have come to the conclusion that low density does not significantly increase the gastric residence time of a dosage form and hence should have no advantage over other controlled-release dosage forms. Timmermans and Moës (1994) have, however, criticized these studies and concluded that floating systems taken after a meal can be expected to offer clear advantages in terms of gastric residence time prolongation and of reduced variability of transit time.

As already mentioned, furosemide is absorbed preferentially in the upper small intestine. Menon et al. (1994) compared (in dogs) the absolute bioavailability of furosemide from a floating

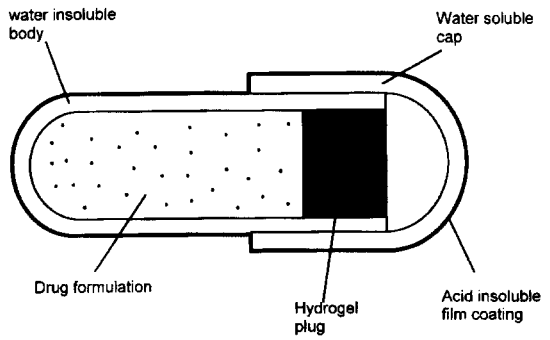

Fig. 6. The enteric Pulsincap®.

dosage form with two commercial products: Lasix® tablets and Lasix® long (enteric tablets). The significant increase obtained in the bioavailability of the floating dosage form indicates the advantage of using a buoyant system. Furthermore, only the floating dosage forms gave satisfactory results with regard to in vitro/in vivo correlations.

It is obvious that prolonging the gastric residence time of a dosage form has no advantage for drugs with wide absorption sites in the gastrointestinal tract. Indeed, although the absorption of isosorbide-5-nitrate (IS-5-MN) administered in pellets is reduced in the colon (Fischer et al., 1987), the bioavailability of IS-5-MN in multiple-unit floating dosage forms is not significantly different from that in control pills when given to beagles (Ichikawa et al., 1991a) (Fig. 5). One should however not conclude from these results that buoyancy has no effect whatsoever, since the same authors found that the bioavailability of *p*-aminobenzoic acid in the same floating pills is significantly increased (Ichikawa et al., 1991a).

It may, however, not be desirable to increase the gastric residence time of drugs such as nifedipine, which is well absorbed along the entire gastrointestinal tract and which undergoes a significant first pass metabolism. The slow gastric emptying may lead to a reduced systemic bioavailability as a result of the gradual exposure of the drug to enzymes on first pass through the intestine and liver (Wilding et al., 1992b).

4.2. Drug targeting in the small intestine

Targeting drug release in the small intestine by means of a pH-dependent coating is required principally to prevent drug destruction by gastric enzymes or by the acidity of the gastric fluid, as well as to prevent nausea and vomiting caused by the irritation of the gastric mucosa due to the drug (Bechgaard and Christensen, 1982; Chamblis, 1983). However, absorption from enteric-coated tablets is erratic and to a high degree dependent on the gastric emptying time (Ritschel, 1991; Hardy et al., 1987; Graffner et al., 1986).

Erythromycin is administered either in enteric-coated dosage forms, in the form of less soluble salts or in the form of prodrugs, as it is thought that this drug has low bioavailability due to hydrolysis in the acidic environment of the stomach (Somogyi et al., 1995; Ritschel, 1991). Somogyi et al. (1995) have shown, however, that apart from gastric hydrolysis there are substantial losses of erythromycin due to others factors. They demonstrated this by comparing the absolute bioavailability of erythromycin when administered in an enteric-coated dosage form and when perfused into the duodenum. Attempts to improve the oral bioavailability of erythomycin beyond 50% by manipulating the formulation are likely to be futile according to these authors. However, a greater consistency in erythromycin absorption both within and between subjects may be obtained with enteric-coated pellets than with enteric-coated tablets (Graffner et al., 1986).

Specific bioadhesive drug delivery systems using lectins have been proposed to improve the oral bioavailability of poorly absorbed drugs such as peptides and proteins through prolonged and/or intensified contact with the intestinal mucosa (Lehr et al., 1992). However, additional experiments have to be done in order to evaluate in vivo their ability to target a specific part of the intestine (Duchêne and Ponchel, 1993; Lehr et al., 1992).

4.3. Drug targeting in the colon

Drugs are generally absorbed to a smaller extent in the colon than in the small intestine. Only

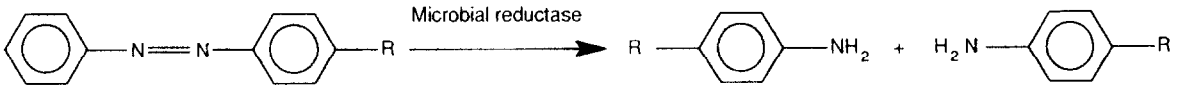

Fig. 7. Cleavage by reduction of the azoaromatic group.

two drugs, nilsodipine and dilazep hydrochloride, are known to be preferentially absorbed in the colon (Antonin, 1993; Staib et al., 1988a; Staib et al., 1988b). It seems, however, favourable to target the drug release in the colon in two cases: for locally acting agents, in order to prevent drug absorption before they reach the action site and for drugs such as peptides, which are metabolized by the endogenous enzymes of the small intestine, since the colon exhibits relatively low digestive enzyme activity (Ashford and Fell, 1994; Saffran et al., 1986; Ritschel, 1991). It should be noted that the time the drug spends in contact with the absorbing surface in the colon may be quite long.

Several physiological factors such as regional pH, gastrointestinal transit time and colonic microflora are used to target the release in the colon for orally-administered drugs.

Ashford et al. (1993) have shown by a gamma scintigraphic study that coatings with polymers which dissolve at a pH greater than 7, such as USP methacrylic acid copolymer type B (Eudragit® S), cannot be used to target a drug in the colon. The enteric coating is capable of protecting a core tablet only in the stomach and the upper small intestine.

Other delayed-release units with a gastroresistant film use the relatively constant small intestine transit time (Gazzaniga et al., 1994a, 1994b); the small intestine transit time seems to be affected neither by food intake nor by the nature of the dosage form (Davis et al., 1986a). Gazzaniga et al. (1994a) describe a system consisting of a drug-containing core coated with two or three polymeric layers. The outer layer dissolves at a pH greater than 5 when the system has left the stomach; the intermediate layer made of hydrophilic swellable polymer, is responsible for the lag phase period and must protect the core during the transit through the small intestine. An inner layer made of an enteric film soluble at a pH greater than 6.5–7 may be added as a further control element. The Pulsincap® systems are based on the same principle (Wilding et al., 1992a; McNeill et al., 1990). These systems are formed from two pieces: the first one containing the drug is insoluble and the second (the plug) is water swellable and swells to liberate the first piece at a predetermined time. The Pulsincap® systems may be designed to release a drug in the colon by coating the plug with an enteric polymer (Fig. 6).

The number of microorganisms is significantly increased in the colon (Table 4). Two main classes of enzymes produced by this population (azoreductases and polysaccharidases) are considered reproducible enough to be exploited in drug targeting (Ashford and Fell, 1994). The use of prodrugs such as azo, glucuronide and dextran conjugates compounds has been proposed to target a drug to the colon (McLeod et al., 1994; Haeberlin et al., 1993; Ryde et al., 1991). This approach seems however to be limited to specific drugs. A more promising approach is to coat the dosage form with agents resistant to gastric and intestinal fluid, but susceptible to bacterial degradation as, for example, azo-linked coatings (Van den Mooter et al., 1994; Van den Mooter et al., 1995; Saffran et al., 1986) or lauric acid dextran esters (Kesslhut and Bauer, 1994). Brondsted and Kopecek (1992) have studied hydrogels containing acidic comonomers and enzymatically degradable azoaromatic cross-links. The azoaromatic group is cleaved by reduction to form a pair of aromatic amines (Saffran et al., 1986) (Fig. 7). The degradability of gels is related to their degree of swelling. In the low pH of the stomach, the gels have a low degree of swelling, which protects the drug against degradation by digestives enzymes. Upon arrival in the colon, the gels have reached a degree of swelling that makes the cross-links accessible to enzymes.

Matrices made of polysaccharides comply with these biodegradation requirements, but they are soluble in water and therefore they have to be transformed into water-insoluble products. This has been achieved for pectin (by forming the calcium salt (Ashford et al., 1994) or by chosing a high methoxy pectin (Ashford et al., 1994; Rubinstein et al., 1993)) or for chondroitin sulfate (by cross-linking (Rubinstein et al., 1992a; Rubinstein et al., 1992b)). It should be noted that the drug has to be released by erosion and a simple diffusion of the drug has to be prevented. Therefore, these types of matrices are only valuable for insoluble drugs.

5. Conclusion

In a review published in 1984, Hirtz (1984) asked the question whether the absorption window is fact or fiction. According to this author, there is only indirect evidence that some drugs are not absorbed along the whole length of the digestive tract. Since this time, many in situ and in vivo studies have been done which concern this question. It appears that there are numerous factors which influence the absorption sites of a drug and which are related to the drug stability and the absorption mechanisms. Although some drugs are absorbed at one site, generally the colon, to a lesser extent than in another, an absorption window in the strict sense of an all-or-nothing nature has not yet been established for a drug until now.

Different information about drug absorption is obtained respectively from in situ and in vivo methods. In order to fully understand how a drug is absorbed into a specific site in the gastrointestinal tract and which factors influence drug absorption, several of these methods should be used together.

Furthermore, the necessity to study drug absorption site along the gastrointestinal tract—which is not predictable—is obvious to develop a new controlled-release dosage form to be administred once a day.

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