BIOPHARMACEUTICAL ASPECTS OF INTESTINAL DRUG ABSORPTION

Prof Reza Fassihi

When a drug delivery system is given orally, its behaviour in the gastrointestinal tract (GIT) can be described in terms of a three-way interaction between formulation, the drug and the gastrointestinal environment. The nature of interactions will change constantly with time as the drug moves along the GIT under the influence of peristalsis. Dissolution behaviour, solubility and absorption rate will all vary in different regions of the tract as a result of changes in gastrointestinal pH, fluid volume, intrinsic permeability of the mucosal membrane and more importantly, pathophysiologic conditions. Gastrointestinal transit rates will be different for solid drug and drug solution, and that will be a further complicating factor in interpreting drug action.

FACTORS AFFECTING GASTROINTESTINAL ABSORPTION

As a rule, about 75% of the drug given orally will be absorbed in one to three hours, but numerous factors can alter this, some physiological and some to do with the formulation of the drug. The main factors are:

1. gastrointestinal motility
2. splanchnic blood flow
3. particle size and drug delivery system
4. chemical factors and drug interactions
5. pathophysiologic conditions.

After passing through the pyloric sphincter, drug reaches, in sequence, the duodenum, jejunum and ileum. These regions have different pH, digestive enzymes and absorptive capacities. The release of food into the duodenum causes the release of cholecystokinin-pancreozymin and secretin by duodenal mucosa, which cause emptying of the gallbladder, secretion of pancreatic enzymes, and flow of pancreatic and biliary fluid. Bile, which has a pH of 7,8-8,6, raises the pH of the duodenal and post-duodenal intestinal contents to approximately 5-7. Bile salts, which are surface-active, can promote dissolution of lipophilic drugs and may also increase membrane permeability of hydrophobic drug molecules through micelle formation and solubilization. It has been reported that bile salts form insoluble nonabsorbable complexes with drugs such a neomycin, kanamycin and vancomycin. Polypeptides such as corticotropin, vasopressin and insulin are also rapidly degraded by the intestinal enzymes and progesterone, testosterone and aldosterone are similarly unstable in the intestine (Welling, 1980; Melander, 1978).

The process of drug absorption from oral formulations involves passage of the drug across the gastrointestinal mucosa, into the mesenteric circulation. In the present discussion, absorption will be taken to mean only the process of passage across the gastrointestinal mucosa into the capillary blood of the mesenteric circulation and not to include the appearance of the drug in the systemic circulation. This distinction is made because between the gut and the systemic circulation lies the liver, the great "poison trap", protecting the systemic circulation from numerous potential toxins which enter the gastrointestinal tract. Evolutionary experience of environmental toxins have provided the liver with an extraordinary range of detoxicating mechanisms for natural toxins which are active in detoxicating mini-drugs. The very presence of the trap, means that for many drugs, all that is absorbed does not enter the systemic circulation intact. This is known as the "first pass effect". Drugs that show a substantial first pass effect in man due to hepatic elimination are listed in Table 1.

Table 1: Drugs showing low oral bioavailability due to extensive first-pass hepatic elimination

Acetylsalicylic acid	Mercaptopurine
Alprenolol	Methylphenidate
Amitriptyline	Metoprolol
Chlormethiozole	Morphine
Coumarin	Neostigmine
Desipramine	Nifedipine
Dextropropoxyphene	Nortryptyline
Dihydroergotamine	Oxyphenbutazone
Diltiazem	Papaverine
Dopamine	Pentazocine
5-Fluorouracil	Phentacetin
Glyceryl trinitrate	Propranolol
Hydralazine	Reserpine
Imipramine	Salicylamide
Isoproterenol	Serotonin
Labetolol	Testosterone
Lignocaine	Tryptophan
	Verapamil

The motility of the small intestine tends to optimise digestion and absorption. There are primarily two types of intestinal movement: peristalsis and mixing. Peristalsis determines intestinal transit rate and therefore the residence time of a drug in the intestine. This will be most important for controlled release dosage forms, enteric coated products as well as those drugs which dissolve slowly or where absorption is maximal only in certain regions of the intestine. Mixing or segmental

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contractions serve to mix and squeeze the food to promote spreading and contact with the intestinal villi. In addition, the muscularis mucosa produces folds in the surface epithelium resulting in an increased surface area and rate of absorption. The villi contract during this process and result in a "milking" action so that lymph flows from the central lacteal into the lymphatic system.

In malabsorption states, or in patients with intestinal resections absorption of some drugs may be impaired (eg, digoxin, thyroxine). In patients with gastrointestinal hurry the absorption of drugs from slow release preparations may be impaired. In such cases an alternative (eg, effervescent potassium salts rather than a slow release preparation) should be used. Gastrointestinal toxicity of drugs can be divided into two groups, according to severity. The first includes less serious effects such as nausea, vomiting and diarrhoea and second, serious effects such as gastrointestinal erosion, bleeding and ulceration. Nausea and vomiting are commonly associated with drugs such as potassium chloride, aminophylline and ferrous sulphate. Potassium chloride also causes the more serious effects of erosion and ulceration, as does aspirin. Some orally administered drugs are more extensively metabolised in the intestine than in the liver. Thus, intestinal metabolism may contribute to the overall first pass effect. First pass effect may so greatly limit the bioabailability of orally administered drugs that alternative routes of administration must be employed to achieve therapeutically effective blood levels. Examples of mucosal metabolism of some drugs are shown in Table 2 (Ritschel 1986).

Table 2: Examples of some drugs for which gastrointestinal metabolism apply

Acetylsalicylic acid	Methadone
Aldosterone	α-Methyldopa
P-Aminobenzoic acid	Pentazocine
P-Aminohippuric acid	Progesterone
Chlorpromazine	Stilbestrol
Clonazepam	Sulfonamides
Cortisone	Terbutaline
Hydrocortisone	
Meperidine	

Note: The drug metabolising enzymes normally associated with hepatic tissue have all been found in the intestinal mucosa of animals and man (Hartiala, 1973). Thus the synthetic reactions (oxidation, reductions and hydrolysis) as well as the conjugation reactions normally associated with detoxication are all catalysed by gut enzymes (eg, Cytochrome P-450, alcohol dehydrogenase, MAO, Dopa decarboxylase, reductases, esterases, amidases, acetylase, sulphokinases, glucuronyl transferases and amino acid conjugates). The lower gut also harbours intestinal microorganisms that are capable of many biotransformation reactions.

The mean transit time of unabsorbed food residues or insoluble granules, pellets, large unit dosage forms and solutions through the human small intestine is remarkably constant and is estimated to be about 4 hr, Figure 1 (Davis *et al*, 1986b). The results of several investigations have revealed that this intestinal transit time in healthy subjects is not influenced by the presence of food, exercise and density of the materials. It appears that physiological discrimination of meal solids and liquids takes place in the stomach rather than the small bowel. However, intestinal transit rate is decreased where there is a reduction in digestive juice secretion and thyroxine secretion, and is increased with diarrhoeal conditions and during insulin hypoglycaemia. Drugs whose absorption can be delayed, decreased or enhanced when taken with meals are listed in Table 3 and 4, respectively.

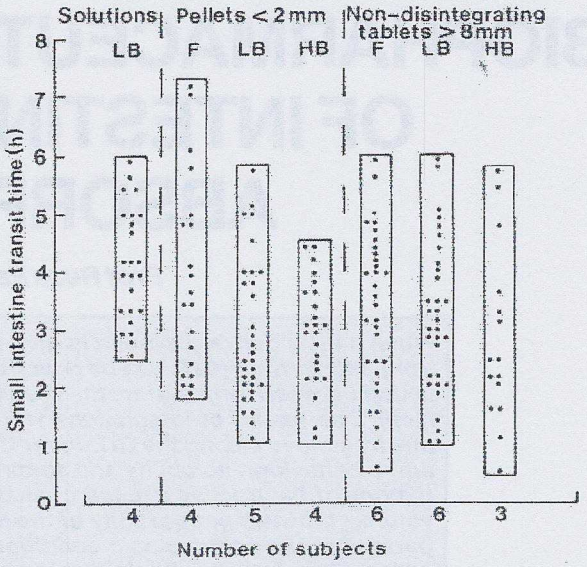


Figure 1: Range of individual data points observed in subjects studied for intestinal transit time of pharmaceutical dosage forms according to feeding conditions using gamma scintigraphy
Key: F — fasted; LB — light breakfast (1500 kJ); HB — heavy breakfast (3600 kJ)
(Data modified from Davis et al, 1986b).

Table 3: Drugs whose absorption can be delayed (Group I) or decreased (Group II) by food or nutrients

Group I*	Group II*
Acetaminophen	Amipicillin
Ampicillin	Penicillins (G, VK)
Amoxicillin	Tetracyclines
Aspirin	Antipyrine
Aiclofenac	Isoniazid
Cephalosporins	Chlorpromazide
Cimetidine	Captopril
Digoxin	Levodopa
Furosemide	Rifampicin
Indoprofen	Lincomycin
Potassium	Propantheline
Metronidazole	
Piroxicam	
Sulfonamides	
Valproic acid	
Quinidine	

**The effects of these drugs will be enhanced when taken on an empty stomach*

Note: There are conflicting reports concerning absorption of drugs in the presence and absence of food and it is difficult to generalize from the information given above. However, delayed absorption in this context means that drug bioavailability is not affected but the onset of action is delayed. Decreased absorption means that drug bioavailability is affected.

Table 4: Drugs to be taken with meals

Acetyl-leucine	Metformin
Acetylsalicylic acid	Methysergide
Aiclofenac	Metiazinic acid
Allopurinol	Metoprolol
Amiodarone	Metronidazole

Azapropazone
Baclofen
Benxbromarone
Benziodarone
Bromocriptine
Carbamazepine
Chloral hydrate
Cinnarizine
Co-trimoxazole
Diazepam
Diclofenac sodium
Dicoumarol
Diftalone
Disopyramide
Ethambutol
Flavoxate
Glibencamide
Glibornuride
Gliclazide
Glipizide
Griseofulvin
Hydralazine
Hydrochlorothiazide
Ibuprofen
Indomethacin
Iron salts
Isoxsurpine
Labetolol
Levodopa
Lidoflazine
Lithium citrate
Minocylcine
Nalidixic acid
Naproxen
Nicotinic acid + derivatives
Niflumic acid
Nifurtoinal
Nitrofurantoin
Oxyphenbutazone
Pancreatin
Pheynlbutazone
Phenytoin
Pivampicillin
Potassium salts
Propranolol
Reserpine
Riboflavine
Spironolactone
Sulindac
Sulphinpyrazone
Theophylline + derivatives
Tinidazole
Tolazamide
Tolbutamide
Tolmetin sodium
Triamterene
Valproate sodium
8-Methoxsalen
5-Flurouracil

Note: the effects of these drugs will be enhanced when taken with meals.

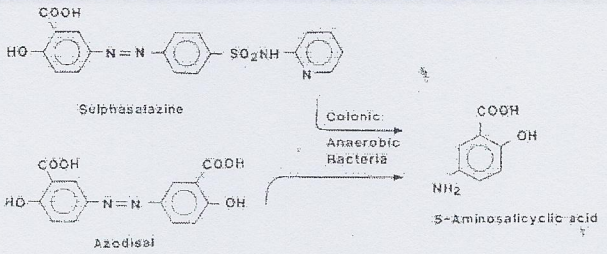


Figure 2: Site-specific drug delivery through selective prodrug bioactivation at the target by azo-reductases of anaerobic colonic bacteria

Recent studies have shown that 5-ASA is the active component which both heals and may reduce the number of relapses in colitis. Sulphapyridine appears to act as the carrier molecule for 5-ASA and is likely to be responsible for most of the side effects and allergic reactions. 5-ASA cannot be simply given orally in the treatment of colitis because it is unstable in acid and is also absorbed by the small intestine and will not reach its target (the colon) in effective concentration. Oral preparations intended to deliver compounds to the human colon have been developed as coated capsules containing 5-ASA and a prodrug form of 5-ASA involving two molecules of 5-ASA linked together with an azo bond which would be split by bacteria in a similar way to sulphasalazine. A specific enteric coated tablet containing 5-ASA in pellets embedded in a dispersible matrix system seems a possibility for the management of ulcerative colitis. Other drugs that are most likely to be presented to the colon for topical release and absorption are salicylazobenzoic acid and steroids such as prednisolone phosphate.

TRANSIT AND DRUG ABSORPTION IN THE COLON

The distal portion of the gastrointestinal tract, the colon, has as its primary function water and electrolyte absorption (proximal half) and the storage of faecal matter prior to its being expelled (distal half). Drug absorption from the colon is likely to be quite slow in comparison with the small intestine because of the small surface area available for absorption.

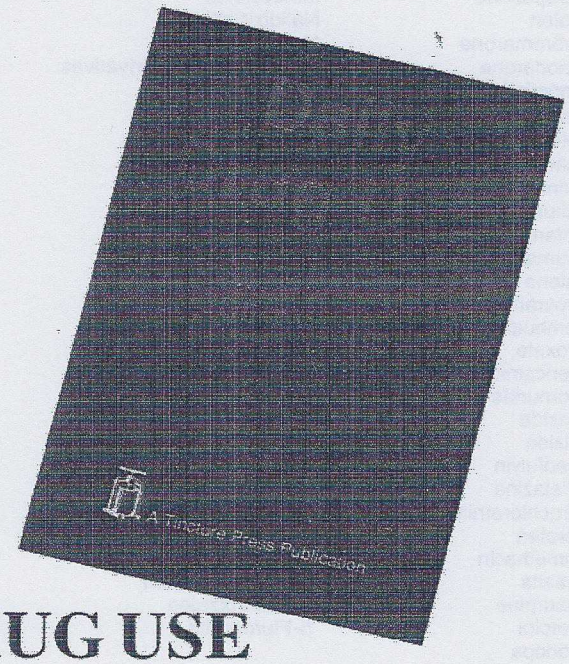
Patients who take non-steroidal anti-inflammatory drugs have an increased incidence of gastric bleeding and peptic ulceration. Thus cases have been reported in which indomethacin delivered in an osmotic pump was associated with intestinal perforation. Single unit dosage forms can be held for long periods (4-12 h) at the ileocaecal valve before moving into the colon. Colon contents are propelled down the tract by a "mass movement", which is similar to the segmenting contractions seen in the small intestine, and occurs only several times a day. The greatest proportion of time in the GI tract is spent by the residues of a meal moving through the colon. In diarrhoea the rate of movement through the colon is fast and fluid absorption is incomplete. The ideal delivery system to the proximal colon should retain the drug within the system for approximately 5-6 hours after administration to the patient, to allow time for gastric emptying and transit through the small intestine and should then disperse and travel through the ascending colon. Oral preparations which are released in the colon would be of particular value in the management of patients with inflammatory bowel disease where the topical action of a drug may be of additional value. Sulphasalazine (salaxopyrin) is the most effective agent to maintain remission in ulcerative colitis. Its use is limited by adverse reactions including allergy, intolerence and male infertility. Sulphasalazine consists of two compounds, sulphapyridine and 5-amino salicylic acid (5-ASA) joined by an azo bond which is split by azo-reductases from colonic bacteria, releasing the constituents (see Figure 2).

BIOPHARMACEUTICAL IMPLICATIONS IN RELATION TO PATHOPHYSIOLOGICAL CHANGES IN GASTROINTESTINAL DISEASE

The pharmaceutical formulation of the drug substances can affect the bioavailability of the drug. We know how the pharmacokinetic and pharmacodynamic processes determine the concentrations of the drug over a period of time at the active site and how pharmacological effect occurs. Now we must examine how these processes interact with the processes underlying the pathology of the disease allowing useful rationalisation and interpretation of drug action.

Steatorrhoea is a condition in which there is an increase in faecal fat excretion as noted in pancreatic disease and occurs in gastrintestinal disorders such as coeliac and Crohn's disease, small bowel diverticulosis, vagotomy, intestinal resection and after ingestion of neomycin and cholestyramine. Subtotal or total villous atrophy may follow chronic treatment with p-aminosalicylic acid, cytotoxic drugs, colchicine, paramomycin, metformin and slow release potassium chloride. Villous atrophy occurs in coeliac disease and dermatitis herpetiformis. Coelic disease is thought to be caused by sensitivity to cereals and food containing gluten and often presents as a malabsorption syndrome. Another factor influencing drug absorption in coeliac disease might be an increase in the pH of the gut lumen or acid microclimate. This might contribute to more rapid absorption of basic drugs, such as propranolol. On the other hand the absorption of practolol is delayed in coeliac disease. The absorption of folic acid is pH dependent and might, therefore, be influenced by changes in acid microclimate in patients with coeliac disease. It is possible that the permeability of the intestinal mucosa to drugs might be altered by disease, but little information is available on this point.

In Crohn's disease there may be extensive thickening of the gut wall, narrowing of the lumen and secondary changes



DAILY DRUG USE

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It is earnestly to be desired that practitioners from a variety of disciplines will avail themselves of this easily accessible information which must enhance the benefits of drug therapy, and diminish the incidence of drug-induced disorders.

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Since the last edition (1985), several new important pharmacological entities have appeared on the South African market. These have been incorporated in this update. Chapter 36 has been extended to include various tables of drug comparisons which I feel may be of use to the prescriber/health practitioner. These include a comparison of the properties of the tricyclic antidepressant agents, phenothiazine tranquillizers, lipid lowering agents and benzodiazepines. The section on geriatric drug use has been rewritten.

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in motility. The effects on drug absorption are variable and unexplained. The absorption of rifampicin is unaltered, that of clindamycin and sulphamethoxazole is apparently increased, while the absorption of erythromycin stearate is reduced.

In small bowel diverticulosis, which is one of the most important pathophysiological conditions in which there is a shift in gut flora to a predominantly anaerobic population which may be resposible for steatorrhoea and malaborption. Although in such circumstances increased metabolism of drugs by intestinal bacteria might be expected, absorption does not seem to be decreased.

Examples of clinically important changes in drug absorption in patients with gastrointestinal disease are as follows: delayed gastric emptying has been shown to be responsible for therapeutic failure of levodopa in patients with Parkinson's disease. Achlorhydria (absence of hydrochloric acid) occurs in pernicious anaemia and is common in the elderly. The resulting changes in pH will influence drug dissolution and possibly gastric emptying rate and so alter the absorption of many drugs. Variable effects of drug absorption have been reported after gastric surgery. Hypothyroidism failing to respond to oral thyroxine or triiodothyronine is an important but rare complication of coeliac disease. The risk of co-trimoxazole induced aplastic anaemia is greatly increased in patients with coeliac disease and folate depletion and osteomalacia is an important risk with prolonged anti-convulsant therapy in coeliac disease. The delayed absorption of many drugs in this condition is unlikely to be of therapeutic significance.

Diarrhoea, with accelerated small intestinal transit may have important effects on drug absorption, particularly with the slowly dissolving or slow release preparations. Indeed, diarrhoea has been held responsible for failure of oral contraception.

MALABSORPTION DUE TO STRUCTURAL AND FUNCTIONAL CHANGES

Many different diseases or their consequences can cause malabsorption either by means of impaired digestion (Table 5), or impaired absorption, (Table 6).

Signs and symptoms associated with malabsorption

1. Manifestations directly attributable to malabsorption: weight loss, glossitis, carpopedal, spasm, absent tendon reflexes, cutaneous bruising, abdominal distension, flatulence, abdominal bloating and discomfort due to increased bulk of intestinal contents and gas production. Dermatitis herpetiformis is often associated with a mild degree of coeliac-like enteropathy. Diarrhoea is not always present. Sometimes steatorrhoea occurs — pale, soft, bulky, malodorous stools, that stick to the side of the toilet bowl, or float and are difficult to flush away. This kind of stool is most likely to occur in coeliac disease or tropical sprue. The stools in chronic pancreatic disease may appear greasy with free floating globules of undigested dietary fat (triglycerides) because of pancreatic lipase deficiency (Merck Manual 1987). Steatorrhoea can be present without florid abnormalities of the stool. Explosive diarrhoea with abdominal bloating and gas after milk ingestion points to lactase deficiency (alactasia). These effects are seen more in the elderly and pharmacist monitoring of drug therapy can play an important role in optimising drug use in the elderly.

2. Manifestations due to deficiencies secondary to malabsorption: the range and severity of nutritional deficiency relates to the severity of the primary disease and the area of the GI tract involved. Many patients with malabsorption are anaemic, usually due to deficiencies of iron (microcytic anaemia) and folic acid (megaloblastic anaemia). Vitamin B_{12} deficiency is uncommon, partly because body stores are considerable, and partly because few disorders cause B_{12} absorption to fall below the daily requirements. Protein malabsorption may lead to hypoproteinemic oedema, usually of the lower limbs. Dehydration, potassium loss and muscle weakness can follow profuse diarrhoea. Calcium deficiency is common and is due partly to Vitamin D deficiency with impaired absorption and partly to calcium binding with unabsorbed fatty acids. This may cause bone pain and tetany. Infantile rickets where osteomalacia may occur in severe adult coeliac disease. Thiamine deficiency (Vitamin B_1) may cause paresthesia and malabsorption of the mainly fat soluble. Vitamin K can lead to hypoprothrombinemia with bruising and bleeding tendency (Merck Manual 1987). Severe riboflavin (Vitamin B_2) deficiency may cause a sore tongue and angular stomatitis, but Vitamin A, C and niacin deficiencies seldom cause clinical problems.

3. Manifestations of malabsorption due to an underlying disease: some diseases that cause malabsorption, have distinctly different clinical presentation, eg, the jaundice of biliary cirrhosis and pancreatic carcinoma, the abdominal angina of mesenteric ischaemia, the boring central abdominal pain of chronic pancreatitis, and the severe, persistent ulcer dyspepsia of the Zollinger-Ellison syndrome (syndrome caused by a gastrin-secreting tumour of the pancreas, producing a high concentration of hydrochloric acid in the stomach; ulcers are formed in the oesophagus and upper intestinal tract).

4. Symptoms associated with the ageing process (elderly): Structural and functional changes in the gastrointestinal tract have particular significance on the effectiveness of orally administered medicines. Gastric acid output and peristaltic activity decrease with age. The result is a relatively high incidence of anaemia necessitating supplementary inorganic iron therapy, which can form non-absorbable iron complexes with tetracyclines and synthetic penicillins if administered concurrently. Slowed gastric muscular activity, decreased emptying time and the rising of the pH of gastric juices may increase the irritating effect of some drugs such as aspirin or phenytoin, because of their extended time in the stomach.

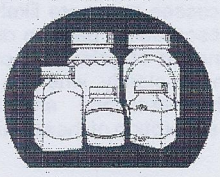

Table 5: Malabsorption due to disease states resulting from impaired digestion

Impaired digestion resulting from	Conditions
Inadequate mixing	Gastroenterostomy Billroth II gastroectomy Gastrocolic fistula
Insufficient digestive agents	Chronic pancreatitis Cystic fibrosis Chronic liver failure Biliary obstruction Alactasia Sucrase-isomaltase deficiency
Improper milieu	Zollinger-Ellison syndrome (low duodenal pH) Bacterial overgrowth-blind loops (deconjugation of bile salts) Diverticula

Table 6: Malabsorption associated with impaired physiological conditions

Impaired absorption resulting from	Conditions
Acute abnormal epithelium	Acute intestinal infections Neomycin Alcohol
Chronic abnormal epithelium	Coeliac disease Tropical sprue Whipple's disease Amyloid Ischaemia Crohn's disease
Short bowel	Intestinal resection for Crohn's disease Volvulus Intussusception Infarction
Impaired transport	Blocked lacteals — lymphoma Lymphangiectasia Addison's disease —? transport enzyme ? Abetalipoproteinemia

Modified from The Merck Manual 15th ed (1987)

Changes in the colon during ageing cause constipation, one of the more troublesome functional problems of the elderly. The result may be overuse of laxatives, which can lead to dehydration, hypokalaemia and reduced absorption of fat-soluble vitamins. Constipating drugs, such as certain antacids, antihypertensives, anticholinergics, antidepressants and the phenothiazines, must, therefore, be used with care in the elderly.

In general, it appears that drugs which are absorbed by specific transport processes are more likely to be affected than those that are absorbed by passive diffusion. The absorption by active transport of galactose, calcium, thiamine and iron is reduced in the elderly, whereas studies of paracetamol, aspirin, phenylbutazone and sulphamethizole demonstrated normal absorption of these passively absorbed drugs in the elderly.

CONCLUSION

With wider appreciation of pharmacokinetic and pharmacodynamic principles and the introduction of therapeutic drug monitoring, a variety of controlled release oral dosage forms has been introduced over the last decade. Controlled constant drug input might provide greater selectivity of drug action and reduced toxicity by avoiding the succession of peaks and troughs of drug concentration associated with conventional therapy. Drug absorption from many of these dosage forms depends on the location of the delivery system in the gastrointestinal tract. Individual differences in the extent of absorption have pharmacokinetic consequences, similar to those arising from changes in dosage form formulation.

As the mouth to anus transit time is typically 1 to 2 days, these data on gastric and small intestinal transit times indicate that, for the majority of this time, ingested solids are in either the large bowel or the rectum. With the physiologic information given, the possible role of gastric emptying and intestinal transit in the absorption of drugs given in solid dosage forms can be understood. Considering that many conventional tablets and capsules, in which the drug dissolves so rapidly that most is in solution before much has entered the intestine, gastric emptying clearly influences the rate of drug absorption. Hastening gastric emptying, for example, quickens drug absorption from solution. Some drugs do not dissolve in the stomach, whereas, in the intestine both rapidly dissolve and pass across the intestinal wall. Gastric emptying then dramatically affects the time and perhaps the rate of drug absorption. An enteric coated product is an extreme example of this situation. On the other hand, some drugs such as griseofulvin, that is sparingly soluble in both gastric and intestinal fluids, there may already be insufficient time for dissolution and absorption when this drug is administered as a solid. With a fixed short time within the small intestine, the slow release of such a drug from the stomach increases the total time it is in the intestine and decreases the concentration at any one site. Both conditions favour increased bioavailability. As mentioned, food, fat in particular, delays gastric emptying, and this delay may be one of the explanations for the observed increase in the bioavailability of griseofulvin when taken with a fatty meal. It appears that physiological discrimination of meal solids and liquids takes place in the stomach rather than the small bowel. Small intestine transit time is remarkably constant irrespective of size of the dosage form, density or presence of food. Single unit dosage forms may be held for long periods at the ileocaecal valve before entering the colon. Transit time of dosage forms is shorter when fibre-containing food is consumed, as dietary fibres affect the digestion process. Subsequently, as the intestinal fluid and contents move into the large intestine and water is reabsorbed, the resulting compaction of the solid contents may severely limit further dissolution and hence absorption of drug.

Chemical factors affecting drug absorption do so by influencing the state of the drug in the intestine. Thus tetracycline antibiotics bind strongly to calcium ion and calcium rich food, (especially milk) prevents their absorption. Similarly, the use of liquid paraffin as a laxative will retard the absorption of lipophilic substances, such as Vitamin K.

Drug absorption in patients with gastrointestinal disease is variable and unpredictable. This variation is often poorly correlated with the site and severity of disease, chemical structure and chemical properties of the drug studied. Overall, the clinical significance of abnormal drug absorption is unknown, but there have been occasional reports of therapeutic failure attributed to this cause (Table 7).

Table 7: Changes in blood levels of some drugs attributed to Coelic or Crohn's Disease

Disease condition	Drugs showing increased blood levels	Drugs showing decreased blood levels
Coelic disease	Aspirin Cephalexin Erythromycin stearate Fusidic acid Propranolol Sulfamethoxazole	Acetaminophen Digoxin Pivampicillin Practolol
Crohn's disease	Clindamycin Sodium fusidate Sulfamethoxazole	Acetaminophen Cephalexin Erythromycin stearate Lincomycin Trimethroprim

To summarise, a large number of factors can influence drug absorption and response. These include: drug delivery systems, drug form, excipients, drug amount, administration schedule, route of administration, physiological factors, such as age, sex, body weight, genetic, nutritional state, disease, pregnancy, gut flora, gastrointestinal motility, renal function, physical activity and dietary factors are also important and they may increase drug absorption or affect drug metabolism, drug excretion, drug receptor site interactions and finally, pharmacological factors can affect drug absorption. Effect of other drugs and food constituents on enzyme induction, enzyme inhibition, protein binding, stomach emptying time, biliary flow, local blood flow, urinary pH, tolerance and environmental factors are all important determinants of drug absorption and response.

REFERENCES

1. Davis SS, Hardy JG and Fara JW (1986b): Transit of pharmaceutical dosage forms through the small intestine, Gut, 27: 886-892
2. Hartiala K (1973): Metabolism of hormones, drugs and other substances by the gut; Physiological Review, 53: 496-534
3. Melander, A. (1978): Influence of food on the bioavailability of drugs; Clinical Pharmacokinetics, 3: 337-351
4. Ritschel WA (1986): Biopharmaceutical data on the GIT, in Handbook of Basic Pharmacokinetics, 3rd ed, Drug Int. Publications, Hamilton IL pp 94-111
5. The Merck Manual (1987): Malabsorption Syndromes, published by Merck & Co, Inc. pp 787-815
6. Welling PG (1980): Effect of food on bioavailability of drug, Pharm Int 1: 14-18