The drug then needs to diffuse across the mucous layer without binding to it, across the unstirred water layer and subsequently across the gastrointestinal membrane, its main cellular barrier. After passing through this cellular barrier, the drug encounters the liver and all its metabolizing enzymes before it reaches the systemic circulation. Any of these barriers can prevent some or all of the drug reaching the systemic circulation and can therefore have a detrimental effect on its bioavailability.

Environment within the lumen

The environment within the lumen of the gastrointestinal tract has a major effect on the rate and extent of drug absorption.

Gastrointestinal pH

The pH of fuids varies considerably along the length of the gastrointestinal tract. Gastric fuid is highly acidic, normally exhibiting a pH within the range 1–3.5 in healthy people in the fasted state. Following the ingestion of a meal, the gastric juice is buffered to a less acidic pH that is dependent on meal composition. Typical gastric pH values following a meal are in the range 3–7. Depending on the size of the meal, the gastric pH returns to the lower fasted-state values within 2–3 hours. Thus, only a dosage form ingested with or soon after a meal will encounter these higher pH values. This may be an important consideration in terms of the chemical stability of a drug or in achieving drug dissolution or absorption.

Intestinal pH values are higher than gastric pH values owing to the neutralization of the gastric acid with bicarbonate ions secreted by the pancreas into the small intestine. There is a gradual rise in pH along the length of the small intestine from the duodenum to the ileum. Table 19.1 summarizes some of the literature values recorded for small intestinal pH in the fed and fasted states. The pH drops again in the colon as the bacterial enzymes, which are localized in the colonic region, break down undigested carbohydrates into short-chain fatty acids; this lowers the pH in the colon to around 6.5.

The gastrointestinal pH may infuence the absorption of drugs in a variety of ways. If the drug is a weak electrolyte, pH may infuence the drug's chemical stability in the lumen, its rate and extent of dissolution or its absorption characteristics. Chemical degradation due to pH-dependent hydrolysis can occur in the gastrointestinal tract. The result of this instability is incomplete bioavailability, as only a fraction of the administered dose reaches the systemic circulation in the form of intact drug. The extent of degradation of penicillin G (benzylpenicillin), the first of the penicillins, after oral administration, depends on its residence time in the stomach and the gastric pH. This gastric instability has tended to preclude its oral use. The antibiotic erythromycin and proton pump inhibitors (e.g. omeprazole) degrade rapidly at acidic pH values and therefore have to be formulated as enteric-coated dosage forms to ensure good bioavailability (Chapter 20). The effects of pH on the drug dissolution and absorption processes are also discussed in Chapter 20.

Table 19.1 pH in the small intestine in healthy humans in the fasted and fed states

Location	Fasted state pH	Fed state pH
Mid-distal duodenum	4.9 6.1 6.3 6.4	5.2 5.4 5.1
Jejunum	4.4–6.5 6.6	5.2–6.0 6.2
Ileum	6.5 6.8–8.0 7.4	6.8–7.8 6.8–8.0 7.5

Data from Gray & Dressman (1996)

Luminal enzymes

The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine in response to ingestion of food. These enzymes are responsible for most nutrient digestion. Pepsins and the proteases are responsible for the degradation of protein and peptide drugs in the lumen. Other drugs that resemble nutrients, such as nucleotides and fatty acids, may also be susceptible to enzymatic degradation. The lipases may also affect the release of drugs from fat/oil-containing dosage forms. Drugs that are esters can also be susceptible to hydrolysis in the lumen.