regimens. The aim of such planning is to ensure that the medicine that is susceptible to complexation has moved from the stomach into the intestine well before the complexing agent is administered. This may involve taking the medicine 30 to 60 minutes before the complexing agent. Once the complexing agent has been taken, it is advisable to wait at least two to three hours before taking medicines that are susceptible to complexation or adsorption (see Label 4 in 'Counselling and cautionary advisory labels for medicines', Section A).

- *Effects on gastrointestinal motility*. Since most drugs are largely absorbed in the upper part of the small intestine[1], any medicine that can modify gastric emptying and gastrointestinal motility can theoretically alter the rate of absorption. Opioid analgesics and anticholinergic agents can slow gastric emptying and can therefore reduce the rate of absorption of other medicines. Conversely, metoclopramide increases the gastric emptying rate and can increase the rate of absorption of other medicines, including paracetamol and diazepam. The clinical significance of this observation is often unclear.
- *Pathological changes to the gastrointestinal tract*. A number of medicines, including antibiotics, colchicine and antineoplastic agents, can cause reversible pathological changes to the gastrointestinal tract. Such changes can reduce the absorption of other medicines.
- *Effects on bacterial flora*. In rare instances, the gastrointestinal bacterial flora are involved in the metabolism of medicines. This metabolism might be altered if the flora are modified through the use of antibiotics. However, the clinical importance of this effect probably does not extend beyond the well-documented interaction between oral contraceptives and antibiotics. It is thought that antibiotics may reduce the efficacy of oral contraceptives by inhibiting the bacterial hydrolysis of oestrogen conjugates secreted into bile. Under normal circumstances, the regenerated oestrogen is absorbed back into the bloodstream and contributes to the medicine's efficacy. However, if the hydrolysis is impaired (due to reduced intestinal bacteria), the blood levels of the oestrogen can decrease. Elevated digoxin plasma levels in some individuals treated with antibiotics, particularly macrolides, were thought to be due to a reduction in pre-systemic metabolism by gut flora. However, more recent evidence suggests that inhibition of P-glycoprotein in the intestinal wall may be responsible.[4]
- *Effects on metabolising enzymes and transporters in the intestinal wall*. Within the intestinal wall, enzymes and drug transporters, particularly CYP3A4 and P-glycoprotein respectively, work together to reduce drug absorption. Where one or both of these are induced or inhibited by co-administered drugs, herbs or food there is the potential for altered bioavailability of a range of therapeutic drugs. In the case of inhibition, the consequences are more likely to be clinically relevant where the drug has a low bioavailability. For example, down-regulation of intestinal CYP3A4 by grapefruit juice causes felodipine bioavailability to significantly increase (from 14% to 25%) in healthy volunteers[5], whereas changes in amlodipine bioavailability are relatively minor (81% to 88%).[6] Induction of intestinal P-glycoprotein by rifampicin and other agents such as St John's wort can lead to significant reduction in the bioavailability of drugs such as digoxin.[7] (See St John's wort in 'Complementary medicines monographs', Section C.)

When assessing the likely impact of a medicine interaction that is mediated via an alteration in absorption, it is important to review the literature to determine whether the interaction will lead to a change in the rate or extent of absorption (or both) of the affected medicine. Alterations in the rate of absorption will primarily be important for medicines that are administered for immediate, short-term effects (analgesics, anti-emetics) since the onset of these effects may be delayed if the absorption rate is decreased. The most common cause of a reduction in the rate of absorption is delayed gastric emptying (a delay in the time taken for an orally administered medicine to move from the stomach into the intestine). Medicines that can delay gastric emptying include aluminium-containing antacids, opioids and medicines with anticholinergic effects.

A reduction in the rate of absorption will not usually lead to a reduction in the extent of absorption (the amount absorbed). A general principle is that the average concentration of a medicine in plasma is affected by alterations in the extent of its absorption but not by changes in the rate of absorption. Therefore, if a medicine is being taken chronically, it is most important to focus on interactions that lead to changes in the extent of absorption. Another general principle is that the plasma levels of medicines that already have a low to medium bioavailability are most likely to be affected significantly by interactions that lead to changes in the extent of absorption. In contrast, medicines for which oral bioavailability is close to 100% under normal circumstances tend to be less susceptible to changes in the extent of absorption.