are designed to be acid resistant. Some patients can have a higher stomach pH due to age, disease or ethnic origin which can affect dosage form disintegration and dissolution. This can result in premature drug release and/or dose dumping (dose dumping is the release of all the drug in one bolus).

Gastrointestinal pH generally increases in the small intestine, due to bicarbonate secretion. This is often used as a trigger for small intestinal drug delivery via gastro-resistant coating. The pH gradually increases to a maximum of about pH 7 at the ileocaecal junction. In the colon, the pH drops slightly due to the production of short chain fatty acids by bacteria here, but gradually rises again distally. In some people, the pH does not get as high as pH 7 (and this may change from day to day). Therefore, if a polymer is used which dissolves at pH 7 (see below), then there is a good chance that the dosage form using this polymer will not dissolve, leaving a tablet intact and the patient without their dose. This has been observed in the clinic with some patients with ulcerative colitis.

Transit time

The time that a dosage form spends in the stomach, small intestine and colon can be critical for some modified-release systems. In the fasted state, the stomach will empty a non-disintegrating (i.e. non-immediate release) dosage form within 1–2 hours (via a clearing motility mechanism known as the migrating myoelectric complex). Ingestion of food delays this mechanism, and modified-release dosage forms can sometime be trapped in the stomach as long as food is present.

The small intestine is the site of absorption for most drugs and although the transit time of a dosage form through this region is normally around 3–4 hours, it can actually be highly variable (from 0.5–9 hours has been recorded). A modified-release dosage form which releases drug very slowly needs to take into account that it may only be at its site of absorption for a few hours.

The colon has a very variable transit time (1–72 hours). Often modified-release dosage forms reach the colon (as they may not have disintegrated in the stomach or small intestine). How effective they will be at this point depends on whether or not the drug is absorbed in the colon.

The clinical implications of this are seen in a study in which an OROS (osmotic extended-release system) tablet was administered (see later for more details on this type of device). In one instance it travelled slowly through the intestine and the patient received a suitable dose (i.e. blood levels were adequate and prolonged). In another instance, it travelled through the intestine in less than 10 hours, and very little drug was available to be absorbed by the patient, leaving them with sub-therapeutic blood drug levels (Fig. 31.4).

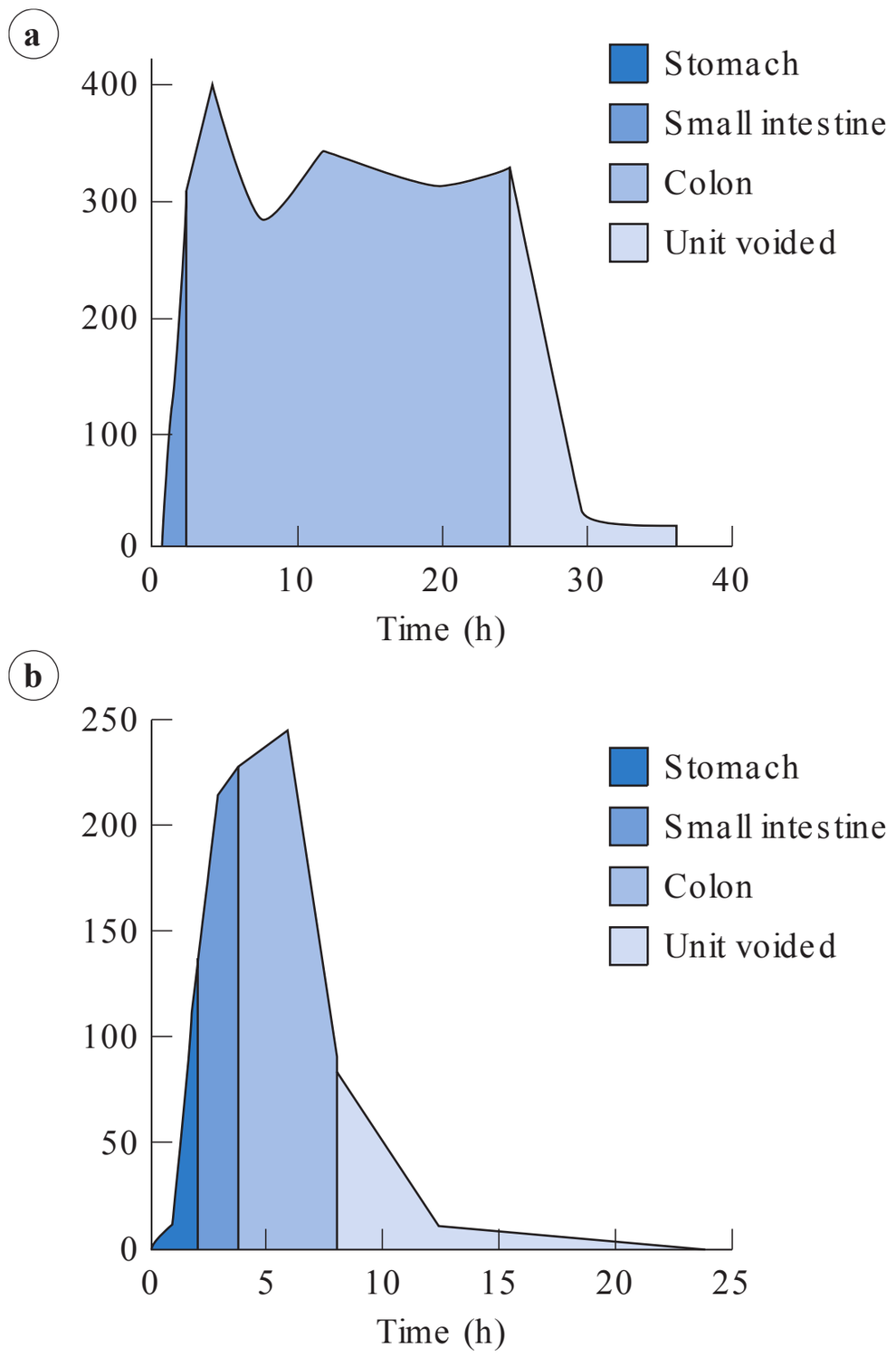

Fig. 31.4 • Plasma concentration-time profles for oxprenolol delivered from an OROS device in an individual, with a long **(a)** and a short **(b)** colon transit time. Courtesy of Washington et al., 2001, with permission.

Fluid

Fluid levels can be highly variable in the stomach, small intestine and colon. In the stomach there may be around 100 mL of total fluid. In the small intestine there is around 50–100 mL of *free* fluid (i.e. that not bound up with digested material, and thus free to dissolve drugs or dosage forms). The colonic contents can be very viscous with only around 10 mL of free fluid actually available. All modified-release dosage forms require the presence