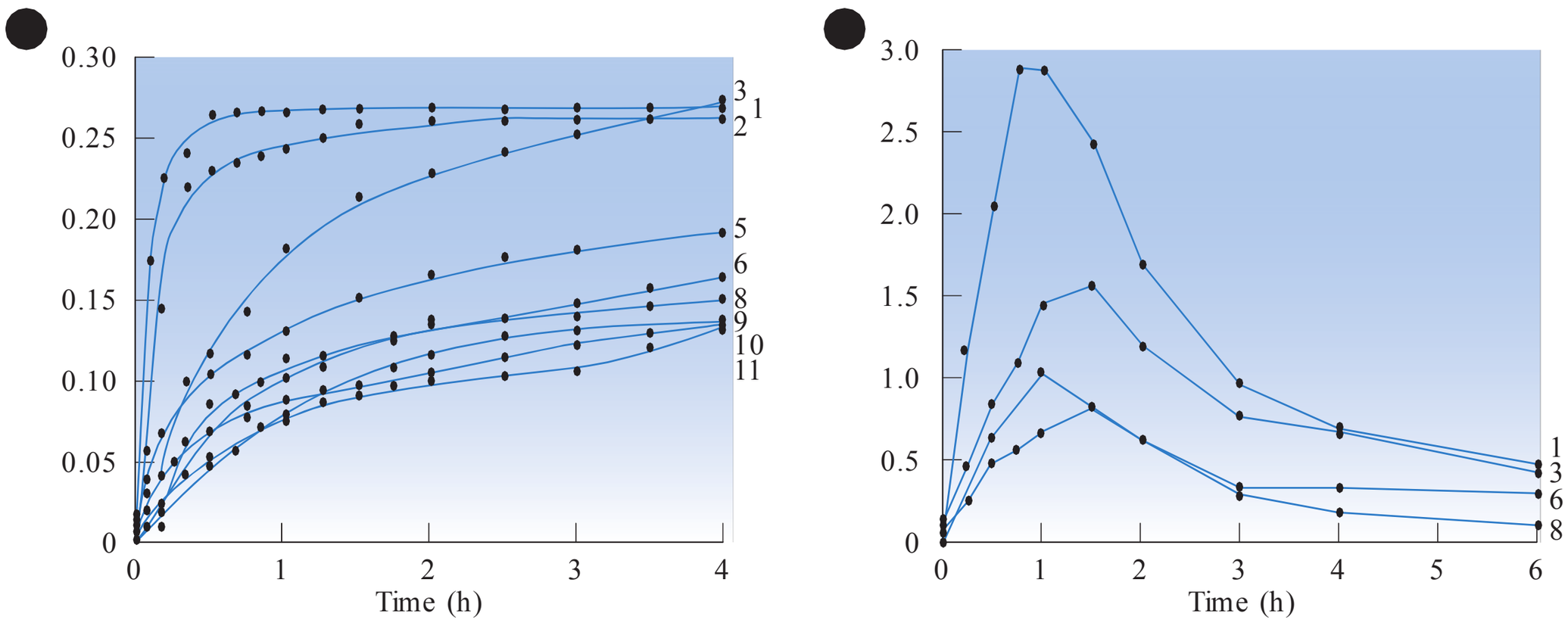

Fig. 35.2 • Dissolution rates of different brands of digoxin tablets available in the UK market at the time of the study **(a)** and corresponding blood (serum) levels of digoxin **(b)**. Formulation 1 ('new Lanoxin') and 8 ('old Lanoxin') are from the same brand, prepared using different manufacturing methods. (Courtesy of Fraser et al, 1973.)

Changes to the release profile and/or dissolution rate of the drug can be brought about by the characteristics of the dosage form and by its method of manufacturing. However, dissolution becomes more complicated if the properties of the physiology of the gastrointestinal tract are taken into consideration (Chapter 19). These must be reflected in any efficient in-vitro test.

pH of the gastrointestinal luminal fluids

As it travels through the gastrointestinal tract, a drug is exposed to increasing pH conditions. Such pH conditions play an important role in the solubility of ionizable drugs, with pK_a values within the pH physiological range (1–7.5), and may affect their bioavailability (discussed fully in Chapter 20). This must be simulated, particularly in predictive dissolution testing (see below).

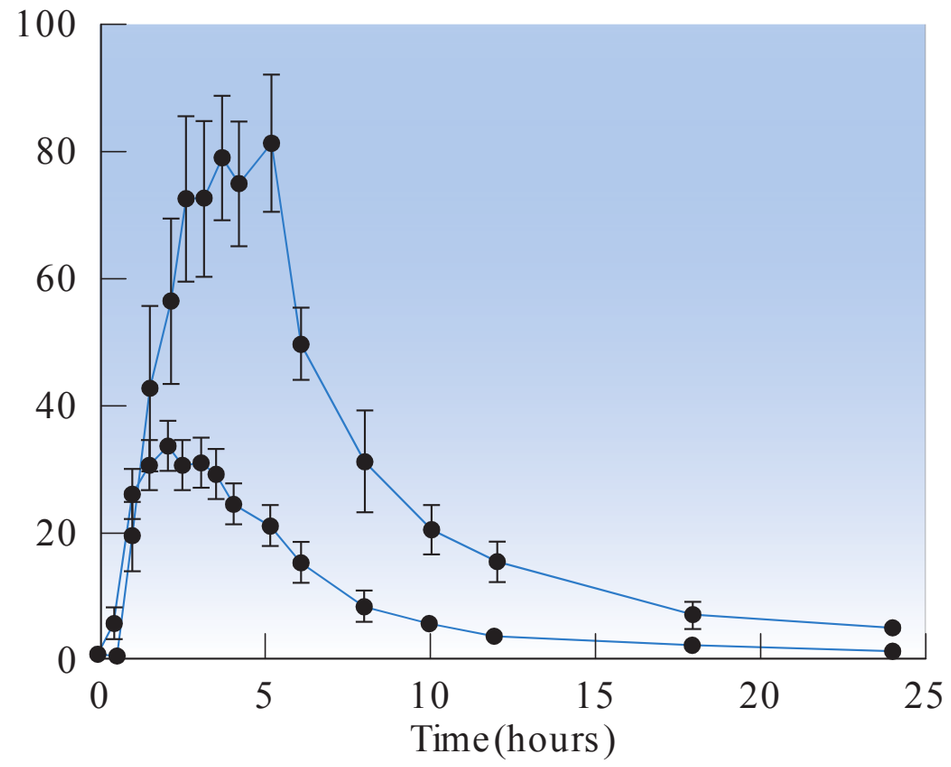

Fig. 35.3 • Plasma concentration-time profiles following administration of 100 mg danazol in a hard gelatin capsule in the fed (–○–) and fasted (–•–) states in humans. (Courtesy of Charman et al 1993.)

Composition of the gastrointestinal luminal fluids

While pH may be sufficiently simulated with buffered solutions, the composition of the gastrointestinal tract fluids is not. Gastrointestinal luminal fluids are enriched with amphiphilic bile components, such as bile salts and lecithin. These substances enhance the dissolution rate of drugs either via an increase in wettability or, at higher concentrations, through the formation of micelles. Although fasted fluids already have wetting and solubilizing effects, this is further increased after a meal, due to increased secretion of bile and to the presence of degradation products of lipids contained in the meal (i.e. fatty acids and monoglycerides). For this reason, the dissolution of poorly soluble drugs is generally higher under fed than in fasted conditions. This is well-exemplified by the lipophilic drug, danazol; as seen in Figure 35.3 the bioavailability of this compound is considerably higher in the fed state.

Two main uses of in-vitro dissolution testing are now discussed further.

- to assess the quality of solid drug products (i.e. using in-vitro dissolution testing as a quality control tool)