

mechanisms, although other mechanisms may occur. Photodegradation of retinol, as well as promoting oxidative reactions, also results in formation of a *cis*-isomer of the molecule around the double bond at position 9. In contrast, degradation occurring in the absence of light causes isomerization at position 13 (see Fig. 48.13).

Chemical incompatibilities

Degradation of a drug may be caused by reaction with another drug present in the formulation or with a formulation excipient.

Hydroxybenzoate ester (parabens) antimicrobial preservatives undergo transesterification reactions with sugars and sugar alcohols, which may be present in a formulation as sweetening agents. For instance, methyl hydroxybenzoate undergoes reaction with sorbitol (Fig. 48.15) to produce a variety of sorbitol hydroxybenzoate esters by reaction with sorbitol's various hydroxyl groups.

A related reaction involves the interaction of aminophylline with suppository bases. Aminophylline is a complex, formed between theophylline and ethylenediamine, which has increased aqueous solubility compared to theophylline alone. On storage of aminophylline suppositories, the melting point of the base increases to above physiological temperature, preventing release of drug. The mechanism for this is the formation of amide bonds between ethylenediamine and the carboxyl groups of fatty acids present in the suppository base. The reaction is the reverse of the amide hydrolysis reaction shown in Figure 48.1b.

Transacetylation reactions have been reported for some drugs. For instance, in tablet formulations that contain aspirin and phenylephrine hydrochloride (a drug used as a nasal decongestant), the acetyl group

is transferred from aspirin to phenylephrine (Fig. 48.16). A similar reaction occurs between aspirin and paracetamol (acetaminophen). Aspirin also reacts with the polyethylene glycol base of suppository formulations, transferring the acetyl group to the polyethylene glycol.

The Maillard reaction involves a reducing sugar and an amine. Reducing sugars tautomerize to an open ring form, containing a reactive aldehyde or keto group. The reaction is responsible for the browning of cooked foods, where the amino group is provided by the protein present in the food. It may also occur between amine-containing drugs and lactose or other sugars employed as a diluent in solid dose formulations. This reaction results in yellowing of white tablets on storage. For example, lactose (Fig. 48.17a) tautomerizes to its aldehydic form (Fig. 48.17b), which reacts with an amine to produce, via several intermediate stages, a coloured l-amino-2-keto sugar (Fig. 48.17c). Other reducing sugars include glucose and fructose. Non-reducing sugars, which do not undergo this reaction, include sucrose and mannitol.

Sodium metabisulphite is commonly added to epinephrine (adrenaline) injection as an antioxidant. However, it reacts with the drug to form epinephrine sulphonate (Fig. 48.18), and this is a significant degradation route for epinephrine.

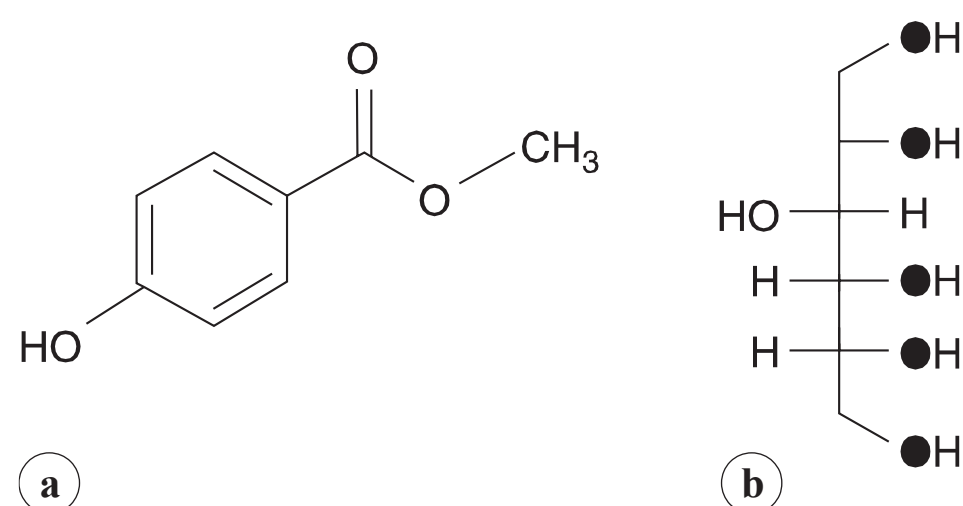


Fig. 48.15 • (a) methylhydroxybenzoate. (b) sorbitol.

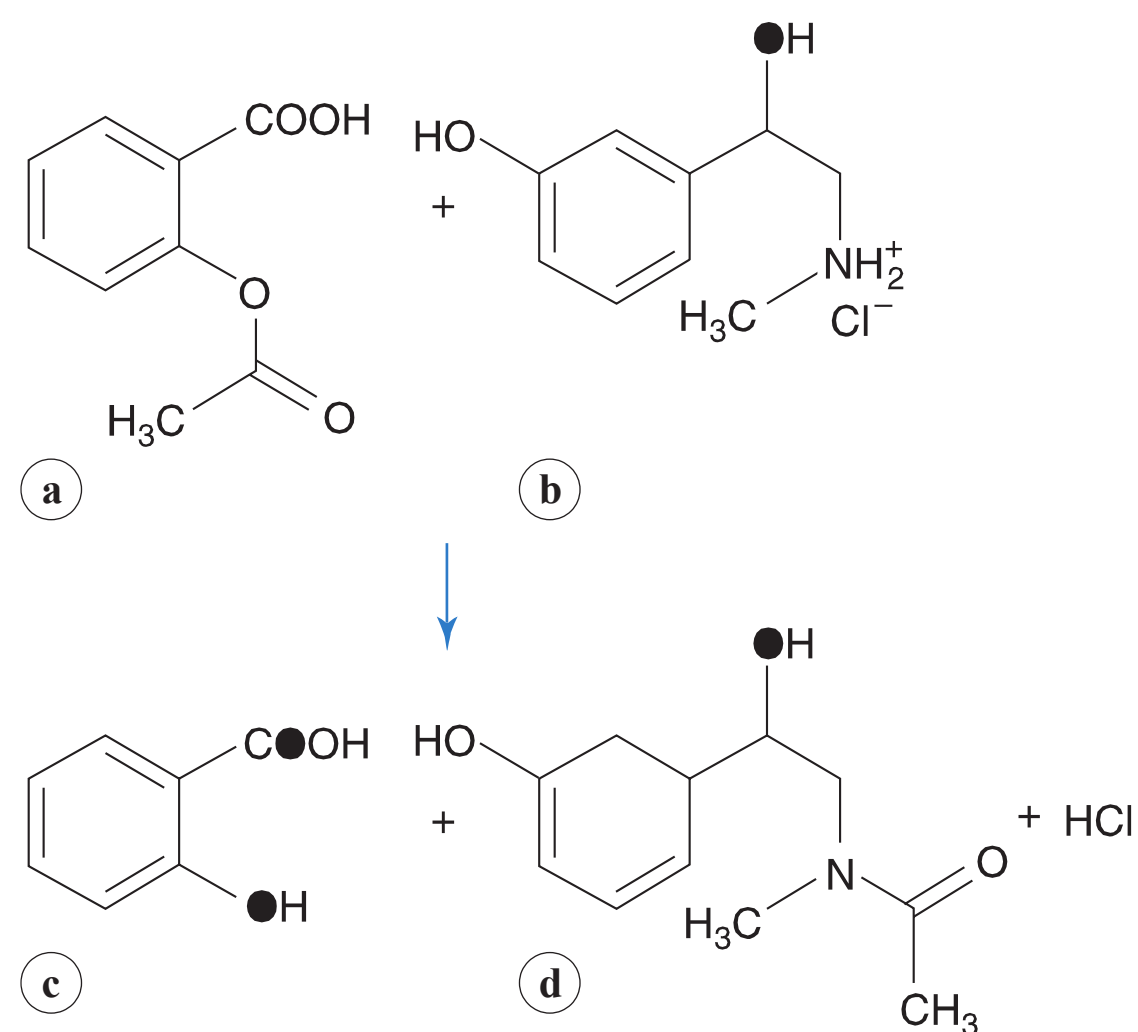


Fig. 48.16 • Transesterification reaction of aspirin (a) with phenylephrine hydrochloride (b) to give salicylic acid (c) and N-acetylphenylephrine (d).