

a pharmacopoeial preservative efficacy test where the manufactured medicine is inoculated with a range of test organisms whose death rate is measured over a 28-day period (see Chapter 14).

Contaminating microorganisms do not invariably grow uniformly throughout a medicine packed in its final market container; they may be concentrated near the surface as a result of the higher oxygen availability there or, in the case of an emulsion, they grow in the water phase rather than the oil. The concentration of preservative available at the site where the organisms are growing is therefore the principal determinant of how effectively the medicine is protected from spoilage, and the 'free' preservative concentration (that which is actually available to kill microorganisms) may be significantly lower than the calculated value. Figure 50.3 shows the major factors that influence preservative activity.

Several groups of common preservatives are affected by pH. This may be a consequence of:

- a change in ionization of the preservative molecule which alters the relative proportions of its undissociated and dissociated forms which possess different intrinsic antimicrobial potencies
- an effect on cell surface charge influencing adsorption of preservative molecules onto the microbial cell
- a change in the solubility or stability of the preservative molecule.

The weak organic acids, e.g. benzoic and sorbic acids, are the most commonly cited examples of preservatives whose ionization and activity are

pH-dependent, but there are several others. These acids are effective in formulations that are naturally acidic or can be buffered to a low pH. This is because in these conditions they exist as the undissociated molecules which are more lipid soluble and more effective than the ionized forms that predominate when the ambient pH exceeds the molecule's pK_a value. Phenolic preservatives exhibit similar but less marked pH dependence. Parabens are also slightly affected in the same way.

This situation contrasts with that seen with quaternary ammonium compounds which are most effective in neutral or slightly alkaline conditions. Bacterial cells are usually negatively charged, and a rise in pH increases the number of such charges and so promotes the binding of positively charged molecules like quaternary ammonium compounds.

Even though many liquid medicines contain a buffer to restrict pH change, it is not uncommon for the product specification to quote a permissible pH range that is sufficiently large to have a significant impact on preservative activity and for the product pH to drift within that range during its shelf-life, which may be 2 years or more. Slow precipitation during storage (e.g. parabens precipitating in falling pH) is a further problem that is not necessarily detected by chemical assays because the assay procedure may re-dissolve the precipitate.

The oil/water partition coefficient is another molecular property that can have a marked influence on preservatives when they are used in emulsions. Since microorganisms grow in the aqueous phase, a preservative that partitions into the oil is essentially inactive, although again, this will not necessarily be apparent because a chemical assay is likely to show

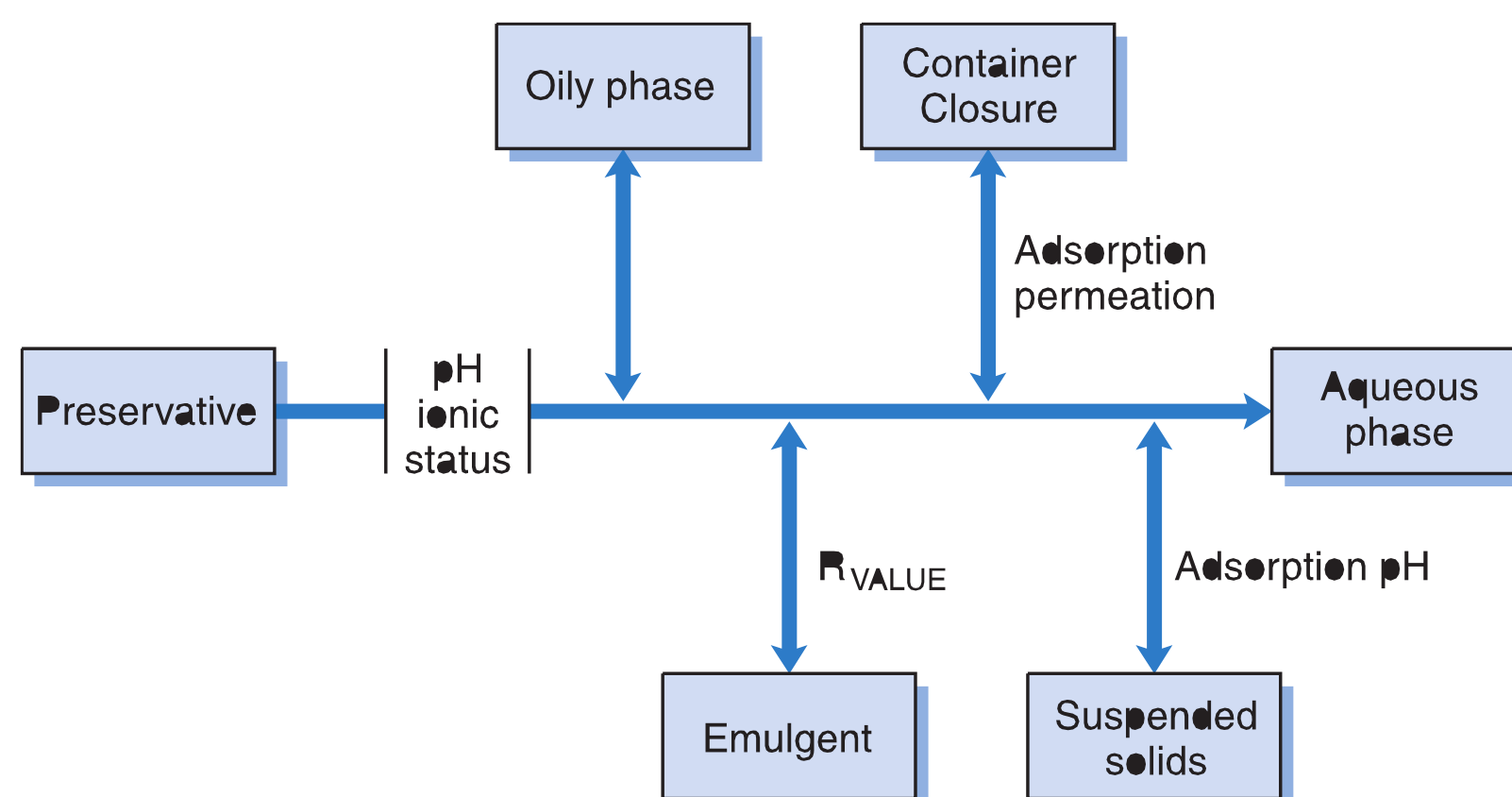


Fig. 50.3 • Preservative availability.