

concentration (thermodynamic activity) of the drug in its formulation. Manipulating skin thickness is difficult, though the application site can be selected as one where the stratum corneum is relatively thin, such as the scrotum that is used to deliver testosterone. Additionally, external forces can be used effectively to circumvent the stratum corneum barrier.

Formulation manipulation

For a given drug in a defined formulation, maximum flux is achieved when the active ingredient is present at saturation (i.e. when C_o , in for example Eqn 39.3, is at its maximum). However, it is feasible to generate supersaturated systems where the drug is present in excess of its solubility. This occurs when, for example, a hydro-alcoholic gel containing a poorly-water soluble compound is applied to the skin. As the alcohol (good solvent) evaporates, the drug can exceed its solubility limit in the remaining aqueous phase and so becomes supersaturated. Supersaturated states are inherently unstable and the excess drug will tend to crystallize rapidly. However, if the formulation is viscous or anti-nucleating polymers are included, then drug crystallization can be inhibited for a period of time, in which case the drug remains in a supersaturated state and provides a greater flux than can be obtained from a saturated solution. In practice, many topically applied formulations are dynamic (gels, foams, creams, etc.) and patches can contain volatile ingredients that may evaporate or partition into skin, resulting in transient supersaturated states.

Supersaturation can also be achieved from co-solvents as shown in Figure 39.8; if solvent A is a 'poor' solvent for the permeant and solvent B is

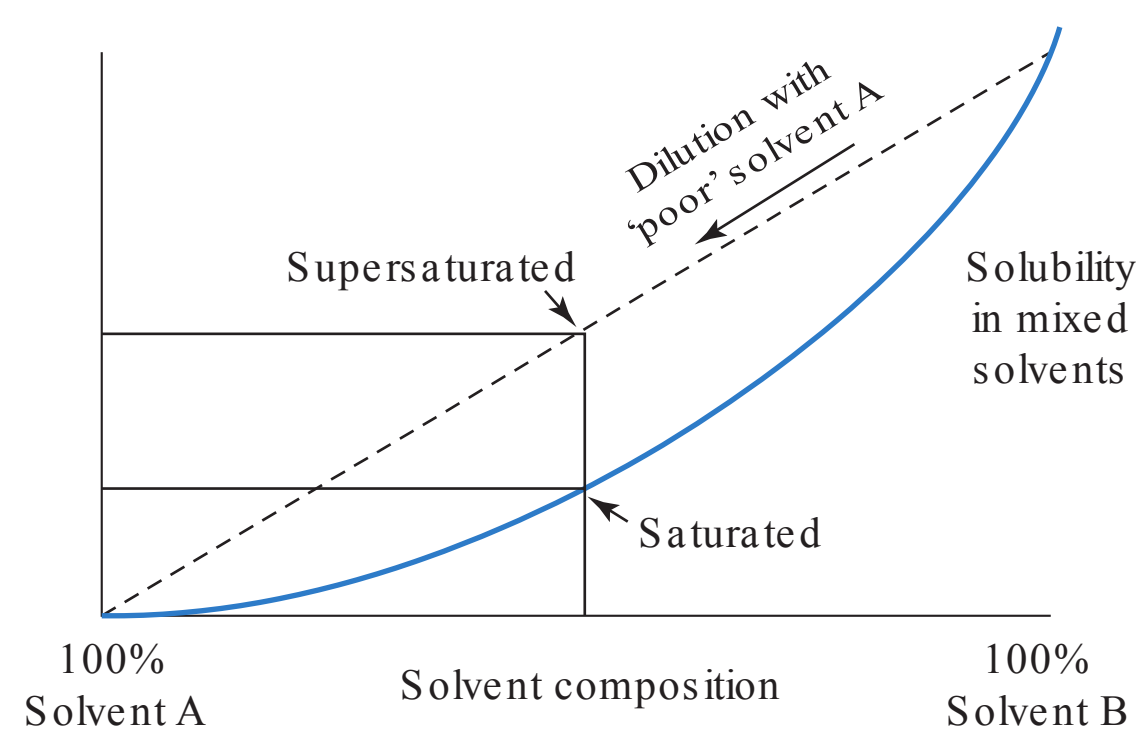


Fig. 39.8 • Illustration of a method to generate supersaturated systems from mixed solvents.

miscible with A but is a 'good' solvent, then the solubility of the drug in mixtures of A and B would follow the solid curve. If a solution of drug in solvent B is then diluted with the poor solvent A, solubility of the drug follows the dotted line and generates supersaturated systems. With time, the drug will crystallize from this supersaturated state to equilibrate with the saturation curve but crystallization can be inhibited by addition of some polymers and this provides a transient increase in drug solubility beyond saturation, hence increasing drug flux.

Other formulation strategies can provide optimal transdermal delivery using the principles described above. For example, formulations should ensure optimal drug release and encourage partitioning into the stratum corneum by using a vehicle in which the drug is only moderately soluble. The active drug should have appropriate physicochemical properties, perhaps by using a pro-drug containing a lipophilic moiety which will enhance partitioning into the lipophilic stratum corneum; ester-linked fatty acids can serve this purpose with the link then cleaved by esterases within the skin, liberating the active principle. Control over pH in the formulation of ionizable drugs is important since ions permeate less well than neutral compounds, or ionic charges can be neutralized by employing ion pairs.

Skin modification

Numerous chemicals, collectively termed *penetration enhancers*, interact with stratum corneum components to increase transdermal drug delivery. These enhancers act by disrupting the highly organized lipid bilayer packing through interacting with intercellular proteins, by increasing partitioning into the membrane or by a combination of these mechanisms. Ideally, penetration enhancers will be pharmacologically inert, will modify the skin barrier in a reversible manner, will be non-toxic, non-irritating, compatible with drugs and excipients and acceptable to patients (good skin 'feel', odourless, colourless, etc.).

The safest and most widely used penetration enhancer is water, and the transdermal flux of most drugs is greater through hydrated skin than through dry tissue. Thus, occlusion is an effective means of increasing the flux of most drugs. Ethanol and other low molecular weight alcohols that are often incorporated into topically applied formulations can also act as penetration enhancers. Ethanol can disrupt