Spoke

Solving Solubility with Science

General Techniques for Preparing Formulations of Poorly Water-Soluble Compounds

In this Brief we discuss water insoluble (lipophilic) compounds and techniques for formulating with them.

Technical Brief

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Introduction

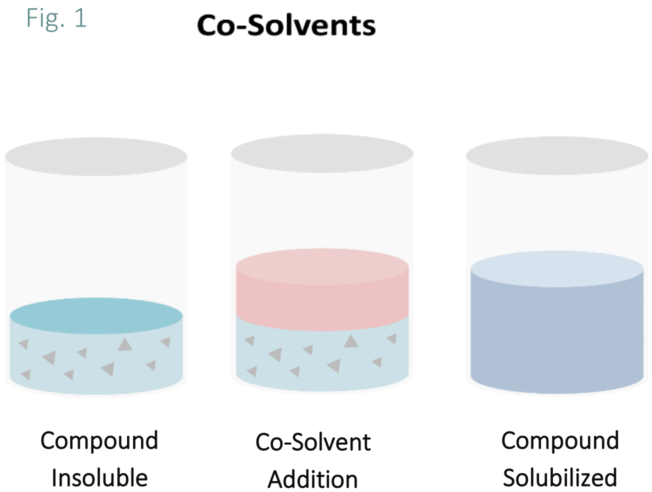
Solubility is a key concern in the delivery of active ingredients in both pharmaceuticals and consumer products. Many desirable functional ingredients for drug products, food, beverages and cosmetics are considered hydrophobic or lipophilic, meaning they are not easily dissolved in water. To understand why solubility matters in how our bodies absorb ingredients, read more here.

Several techniques can be used to allow for the incorporation of these poorly water-soluble compounds into formulations and to improve their uptake and delivery to the consumer. These methods are briefly summarized here. Check back for future technical briefs where we dive in deeper on each of these categories.

Co-Solvents

A co-solvent is a substance that can be added to water to aid in dissolving a hydrophobic compound to form a true solution. Common co-solvents that are miscible (in other words, mix completely) with water include alcohols (for example, ethanol), glycerol, propylene glycol and polyethylene glycols (for example, PEG 400). Selection of an appropriate co-solvent will depend on the ingredient to solubilize and the intended route of administration such as oral (taken by mouth), topical (applied to the skin) or parenteral (given by injection). The concentration of the co-solvent permitted for that delivery pathway may also help narrow down which is the best option to use as some co-solvents are only allowed in products in small amounts (see Fig 1).

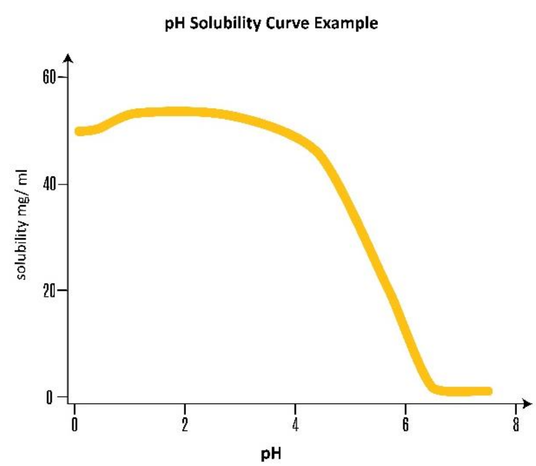
Fig. 1



pH Adjustment/Salt Forms

Some poorly water-soluble compounds may not dissolve in water at neutral or physiological pH (pH of the body is around pH 7.4), however they may potentially dissolve in an aqueous solution with more acidic or basic pH (see Fig. 2). The stability of the dissolved molecule at low or high pH should be considered with this approach – does exposure to acid or base cause that compound to breakdown? Similarly, different salt forms of a compound may be explored that allow for improved dissolution compared to the free acid or free base version of the molecule. These salt forms can be made by ionic interactions between the compound and a counterion, in other words using the positive or negative charges on a molecule.

Fig. 2



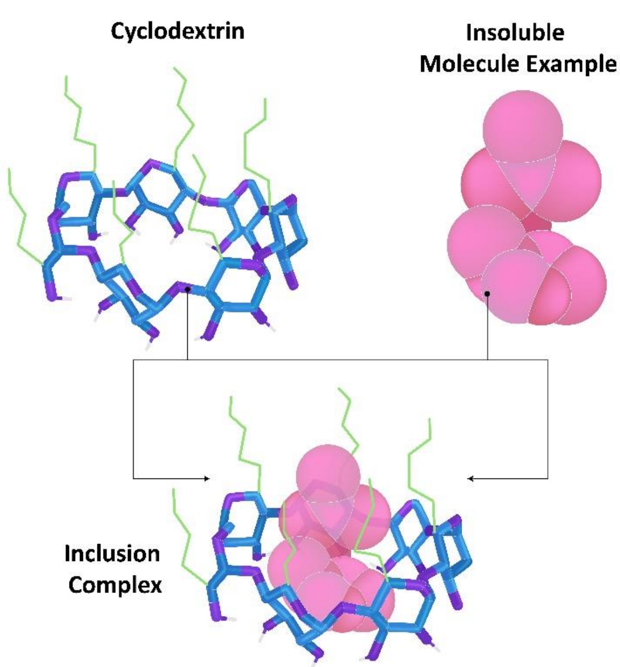
Particle Size Reduction

Particle size reduction is a common method that can be used for improving dissolution rate and dispersibility of hydrophobic compounds. With this technique, individual particles of a compound can be reduced by any of a number of milling methods, typically to a low-micron or nanometer size range. This size reduction allows for the particles to be more easily dispersed or distributed in an aqueous liquid. The increased surface area of the smaller sized particles also may allow for faster dissolution – that is, the small particles will dissolve faster than larger particles of the same material.

Cyclodextrin Complexation

Cyclodextrins are a class of carbohydrate polymers that, on a microscopic level, can form a cup-shaped structure that can "hold" lipophilic actives. This technique allows for relatively low amounts of the poorly water-soluble compound to be sequestered into the hydrophobic portion of the polymer, while the hydrophilic portion of the polymer allows the entire structure to be dispersed into water . This process of the cyclodextrin and the active compound joining together is known as complexation, a way of describing how the two parts now form one new "complex" (See Fig 3).

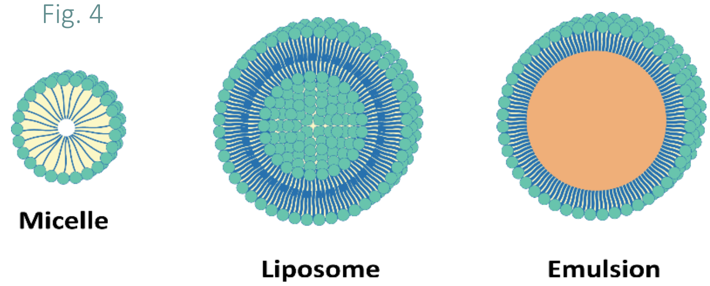
Fig. 3



Liposomes/Micelles

Liposomes are designed to carry actives in a spherical, bilayer, lipid-based shell, while micelles are single layer structures of associated surfactant molecules. In both systems, the hydrophobic ingredient is incorporated into the core or layer of the structure that is "oily", allowing the ingredient to be hidden from the water phase (see Fig. 4).

Fig. 4



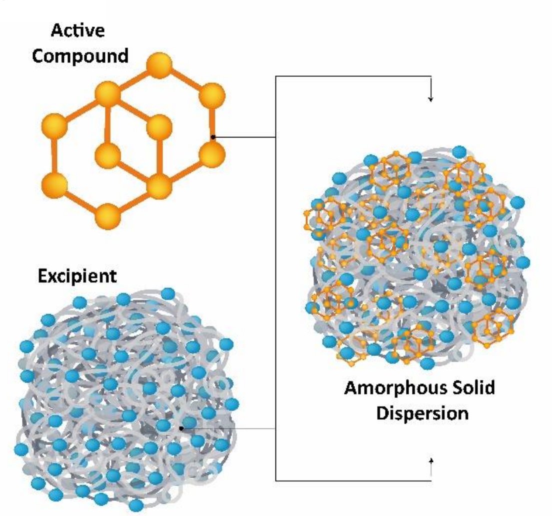
Emulsions

Emulsions are a mixture of oil, water and surfactants. The surfactant allows droplets of oil to form in the water and remain separated. Similar to liposomes and micelles, a lipophilic compound will associate with the oil phase of an emulsion. Selection of both the best oil and associated surfactants will determine the stability of an emulsion-based system (see Fig. 4).

Solid Dispersions/Solid Solutions

Another method of enhancing solubility relies on the use of a solid excipient (inactive ingredient) matrix. This may be to form a solid dispersion (where the hydrophobic compound is dispersed throughout the other solid ingredients) or solid solution (where the hydrophobic compound is dissolved in the solid matrix). Most often these systems allow for an amorphous (non-crystalline) form of the compound to exist in the matrix, which will be more readily soluble in an aqueous environment (see Fig. 5).

Fig. 5



Chemical modification

Finally, instead of working with the desired compound directly, it is possible to alter the chemical structure of some molecules in ways that make them more water soluble. This is often accomplished by adding a more water-soluble component to the functional ingredient, not simply by mixing the two components but to chemically change the molecule. While this method can be beneficial for some molecules, there are additional challenges associated with this technique as studies must be done to understand how this new molecule functions when consumed, as it may lose its functional benefit. Additionally, the new molecule will likely be required to undergo years of testing before it is deemed legal to use by a regulatory agency such as the FDA in the USA.

Glossary of terms in this brief

Aqueous – Of or containing water as a solvent.

Dispersibility or **dispersion** – A term used to describe one compound that is dispersed or "scattered" within an environment, especially an aqueous environment, but is not dissolved.

Dissolution – The act of dissolving in a solvent.

Excipient – Inactive ingredient used to help deliver an active or functional ingredient.

Functional ingredient – An ingredient that provides a health or wellness benefit to the consumer.

Hydrophilic – Describes a compound that is attracted to and most often easily soluble in water.

Hydrophobic – Describes a compound that is not soluble in water.

Lipophilic – Another term for a compound that is not soluble in water but is soluble in fats or oils.

Spoke solves the solubility problem

At Spoke Sciences, we solve the solubility problem, giving you the ability to create the functional consumer product you want. Please contact us if you would like to learn more.