Frequently, a simple approach of pH adjustment or cosolvent is not enough to achieve the target concentration. Cosolvents are often used in combination with pH adjustment to further enhance the solubility. Using this approach, Lee et al. (2003) observed that nearly 85% of Pfizer, Ann Arbor discovery compounds ($n > 300$) submitted for discovery and preclinical injectable formulation development in the year 2000 could be formulated by pH adjustment, cosolvent addition, or a combination of the two approaches. It was also observed that 11% of compounds were not formulatable using this approach, and another 32% of the formulation used more than 55% cosolvent. The high solvent content can limit the pertinent safety assessment of lead compounds. Therefore, the synergistic combinations of pH adjustment and cosolvent are not sufficient to develop commercially viable formulations for water-insoluble drugs. This leads to additional formulation technologies such as complexation, incorporation into micelles, nanosizing, and so forth, being employed in early discovery stages.

The most commonly used solvents for early-stage discovery formulation are polyethylene glycol 400 (PEG-400), propylene glycol, ethanol, glycerin, DMSO, dimethylacetamide (DMA), and *N*-methyl-2-pyrrolidone (NMP). PEG-400 has wide applications across several therapeutic areas for both oral and parenteral administrations. Higher molecular weight PEGs have melting points above room temperature and are viscous, while molecular weights lower than that of PEG-300&400 can be poorly tolerated in *in vivo* studies.

One of the disadvantages of cosolvent systems is their precipitation behavior when diluted with water or aqueous body fluids. Precipitation of drug could potentially occur during *in vivo* testing, which in turn could result in reduced bioavailability. In injectable formulation, this leads to drug precipitation at the injection site, causing injection site irritation. Although in the discovery phase it is preferable to use low volume, high-concentration cosolvent formulations to increase solubility and hence the amount of drug dosed, this practice have increased risks of hemolysis and tissue irritation when administered intravenously. Therefore, cautions need to be taken not to exceed the toxicity levels for the cosolvent. Based on vastly different physical and chemical properties of a wide range of new chemical entities, formulation scientists typically need to consider the molecular structure and consult with members of their therapeutic team to choose appropriate solvents for a particular pharmacokinetic/pharmacodynamic model. For example, high concentrations of ethanol may be unsuitable for CNS-related programs owing to its intoxicating effects. The hemolytic effect of propylene glycol (Krzyzaniak et al., 1997) might render it a liability for cardiovascular programs. Potent cosolvents, such as NMP and diethyleneglycol-monoethyl-ether (Transcutol), often display serious tolerability issues (e.g., drowsiness) in acute and/or chronic animal studies (Maas et al., 2007).

The water-immiscible solvents including the long-chain triglycerides such as peanut oil, corn oil, soybean oil, sesame oil, olive oil, hydrogenated vegetable oils, hydrogenated soybean oil, and the medium-chain triglycerides derived from coconut oil and palm seed, provide another approach to solubilize pharmaceutical compounds. These oily formulations are mainly for oral administration as oral solution or filled into soft-gelatin capsules. Surfactants may be needed for optimal performance of oil formulations.

Complexation

Complexation using cyclodextrins (CDs) is another approach that can be used for solubilization. CDs are a family of cyclic oligosaccharides, the most common α, β, and γ, consisting of 6–8 d-glucopyranosyl units, presenting a hydrophilic outer surface and a lipophilic cavity to which a hydrophobic guest molecule can complex (Szente and Szejtli, 1999). Different numbers of glucopyranose units lead to different cavity sizes. The inner diameter of the hydrophobic cavity is approximately 4.7–5.3, 6.0–6.5, and 7.5–8.3 Å for α-CD, β-CD, and γ-CD, respectively (Loftsson and Brewster, 1996). With lipophilic inner cavity and hydrophilic outer surface, CDs are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes