2 Solubility Theory

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INTRODUCTION

Solubility is the concentration of the solute in a solution when equilibrium exists between the pure solute phase and the solution phase (Huang and Tong, 2004). At low concentrations, solubility is difficult to measure analytically, and at high concentrations, solubility is not an issue in the discovery process (Johnson and Zheng, 2006). If drug solubility is greater than 65 μg/mL, Lipinski et al. (1997) claimed that the absorption of the drug will not be limited by solubility, but a solubility of less than 10 μg/mL will introduce bioavailability issues. Knowledge of the solubility of a drug in water can be critical in formulating products, developing analytical methods, and evaluating drug transport or distribution problems. The approaches presented in this chapter are ideal solution theory, regular solution theory, and the Hansen solubility approach. Of these three, the only one that was developed to describe solutions involving polar species was the Hansen approach. As the reader will discover, however, the Hansen approach is principally based on regular solution theory, which, in turn, was derived from ideal solution theory. Thus, one cannot consider the Hansen solubility approach without some background in the previous theoretical discussions of solubility behavior.

This chapter begins with a description of ideal solution theory because ideal behavior is the reference point by which all other solution behavior is judged. Understanding the properties of real solutions relies on the ability to describe why particular behavior is nonideal. Regular solution theory best describes solution behavior of nonelectrolytes in nonpolar solvents where the enthalpy of mixing is not negligible. The Hansen approach opens up the possibility of describing enthalpic contributions resulting from interactions involving dipoles and hydrogen bonding. It can therefore be applied with some success to the description and prediction of solution behavior involving polar solutes in polar media.