

INTRODUCTION

Despite significant effort and progress in improving the developability of drug candidates, poor aqueous solubility remains to be one of the major challenges to formulation scientists as nearly 40% of marketed drugs and 90% of molecules in the discovery pipeline are poorly water-soluble (Kalepu and Nekkanti 2015). As one of the most well-studied traditional solubilization techniques, complexation has also been used to increase drug stability, reduce gastrointestinal drug irritation, and so on (Szekely-Szentmiklosi and Tokes 2011). In the recent years, the increased applications of cyclodextrins (CDs), cyclic carbohydrates known to form complexes with hydrophobic drugs, and the successful approval of CD-containing products have resulted in increased interest in this technology. The objectives of this chapter are to discuss some theoretical and practical considerations in applying the complexation technique, and to review the recent applications of CD-based complexation.

BACKGROUND

DEFINITIONS

A complex is a species of definite substrate (S)-to-ligand (L) stoichiometry that can be formed in an equilibrium process, in solution, and also may exist in the solid state (Connors 1990). This definition can be expressed succinctly in the following chemical equation for the formation of a complex S_mL_n .



The distinction between substrate and ligand is arbitrary, and is made solely for experimental convenience. Normally, stoichiometric ratios are expressed in the order substrate: ligand, so that 1:2 stoichiometry denotes SL_2 , 2:1 means S_2L , and so on.

TYPES OF COMPLEXES

Based on the type of chemical bonding, complexes can generally be classified into two groups (Connors 1990):

Coordination complexes: These complexes are formed by coordinate bonds in which a pair of electrons is, in some degree, transferred from one molecule to the other. The most important examples are the metal-ion coordination complexes between metal ions and bases.

Molecular complexes: These species are formed by non-covalent interactions between the substrate and ligand. Among the kinds of complex species included in this class are small molecule-small molecule complexes, small molecule-macromolecule species, ion-pairs, dimers and other self-associated species, and inclusion complexes in which one of the molecules, the *host*, forms or possesses a cavity into which it can admit a *guest* molecule.

The classification of complexes into various types is somewhat arbitrary. They can also be classified based on the types of species involved and the nature of interaction forces (Repta 1981). In addition to typical binary complexes, ternary complexes are supramolecular systems composed of three different molecular entities whose third component, as an auxiliary component, in conjunction with CD, further improves desired properties of a drug product (Lokamatha et al. 2010; Kurkov and Loftsson 2013). Most pharmaceutically useful systems are inclusion complexes and molecular complexes between small molecules. Therefore, these will be the topic of this chapter.