15 Pharmaceutical Salts

Steven H. Neau and Nikhil C. Loka

CONTENTS

INTRODUCTION

In formulation development or in the *in vivo* performance of a dosage form, the occasion may arise when the inherently low aqueous solubility of a drug does not meet the solution concentration required. If the solubility of a drug is less than 10 mg/mL, bioavailability or absorption problems are likely to exist (Greene, 1979). If the drug to be formulated as a liquid product possesses an ionizable group, adjustment of the pH in which the drug is to be dissolved might be sufficient to enhance the solubility. This is understandable since there are strong interactions between the solute ion and the ions and dipoles of water, likely overcoming the drawback of a large hydrophobic portion of the drug molecule. However, to become ionized, acidic or basic drugs might require extremes in pH that are outside acceptable physiological limits, or at which stability problems arise (Anderson, 1985; Ansel et al., 1995). In general, aqueous solubility is limited by polarizability, lipophilicity, and the electron arrangement of the drug (Bergström et al., 2007), and salts represent the class of drugs that are most likely to attain the desired extent of solubility in water owing to their increased polarizability (Motola and Agharkar, 1984). A pharmaceutical salt is an ionizable drug presented in a neutral complex with a counterion (Patel et al., 2009). By producing a salt form of a drug, its chemical stability, manufacture into drug products, handling, and administration might be improved, but it is expected that its pharmacokinetics profile is likewise altered (Patel et al., 2009). Furthermore, solid state properties might halt pursuit of certain salt forms mostly due to the influence of these properties on solubility and stability (Ravin and Radebaugh, 1990; Ando and Radebaugh, 2000; Huang and Tong, 2004).

Approximately half of drugs approved for use in the United States are salts (Patel et al., 2009; Thackaberry, 2012). This is not surprising since an ionizable functional group on a drug molecule provides an opportunity for it to engage in an electrostatic, or Coulombic, force of attraction with an oppositely charged ion, with its counterion in a salt form, or with the dipole of water. If that force of attraction can be retained through the crystallization process, a salt product will be obtained (Bhattachar et al., 2006). The salt form of a drug is usually substantially more soluble than the non-ionized form in an aqueous medium, although it should be noted that not all salts have an improved solubility in water when compared to the uncharged form of the drug. Procaine penicillin is often cited as an example of a poorly soluble salt (Amidon, 1981). Nevertheless, salt formation is a simple,