

# Handbook of Pharmaceutical Analysis

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hydrogen chloride gas upon heating or under reduced pressure (lyophilization). Although hydrochloride is commonly used for salt formation, other salts may be better alternatives in the long run.

### C. Salt Preparation

Salts can be produced on a small scale using a variety of methods. Selected methods are described below.

#### 1. Salt Formation from Free Acid/Base

In salt formation from free acid or base, the free acid/base of the drug substance is combined with the base/acid containing the desired counterion in specific molar ratios in a suitable solvent system. There must be adequate solubility of each reactant in the solvent system chosen. The product can be isolated in different ways, often simply by evaporation of the solvent.

#### 2. Salt Formation by Salt Exchange

For salt formation by salt exchange, the salt of the drug substance is combined with a salt containing the desired counterion in specific molar ratios in a suitable solvent system. As described above, there must be adequate solubility of each reactant in the solvent system. If the desired salt of the drug substance is less soluble than the starting materials, it will precipitate out and can be isolated by filtration. If no precipitate is obtained, other isolation methods can be employed. A method that was described for iodide salts (19) involved precipitation of the unwanted counterion first. In this case silver salts were used for the counterions (silver sulfate, silver *ortho*-phosphate, silver lactate) and a silver iodide precipitate was isolated first by filtration. The desired salt of the drug substance was then precipitated from the filtrate by addition of an antisolvent.

#### 3. Other Reported Methods

Variations of the traditional methods for salt preparation described above have been reported. To produce the hydrochloride and hydrobromide salts of the anes-

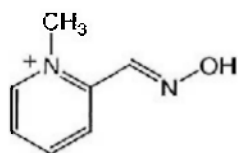


**Fig. 15** The structure of *N*-methyl pyridinium-2-aldoxime.