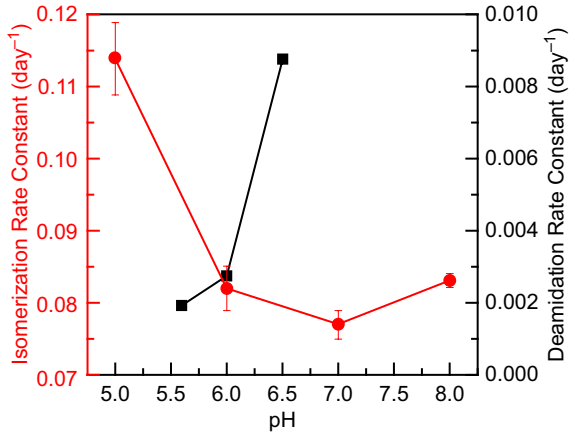

Figure 4.3 The pseudo first-order rate constants for deamidation and isomerization in an IgG1 mAb as a function of pH.
From Shire, Liu, Fries, Matheus, and Mahler (2010).

easy development process. Reviews of common excipients and their function in a formulation are available (Nema, Washkuhn, & Brendel, 1997; Pramanick, Singodia, & Chandel, 2013; Wang & Kowal, 1980). A brief summary of excipients and function in a liquid protein, mAb formulation are now discussed.

Buffers for pH control

Many of the degradation pathways such as deamidation and Asp isomerization are pH dependent (Figure 4.4), and thus excipients need to be added that control the pH. Some of the most commonly used buffers for pH control include acetate, citrate, succinate (pH 3–6), phosphate, histidine (pH 6–8), Tris, and carbonate (>pH 8). The buffer concentration is usually kept low (10–30 mM) to provide enough buffering capacity for control of pH while allowing the solution pH to change rapidly upon administration. Buffer salts such as Tris have fairly large temperature dependence of the pKa ($\Delta pKa/\Delta T°C = -0.028$) and this needs to be taken into account when preparing formulations. Thus, if a Tris buffer system is prepared at 25 °C, the pH of the solution during a recommended storage of 5 °C will be different. Some buffer salts such as disodium phosphate are prone to crystallization upon freezing, and this impacted the stability of a protein during freezing and thawing (Pikal-Cleland, Rodriguez-Hornedo, Amidon, & Carpenter, 2000). The impact of buffer ion on stability of a protein has also been observed. The aggregation of an IgG_1 mAb without the presence of any other stabilizers showed that histidine provides additional stability when compared to other buffering ions (Figure 4.4). The pH does not appear to be a major contributor when considering different buffer species since buffer systems with the same pH (formulations B, C, and D in Figure 4.4) still show significant differences in stabilization.