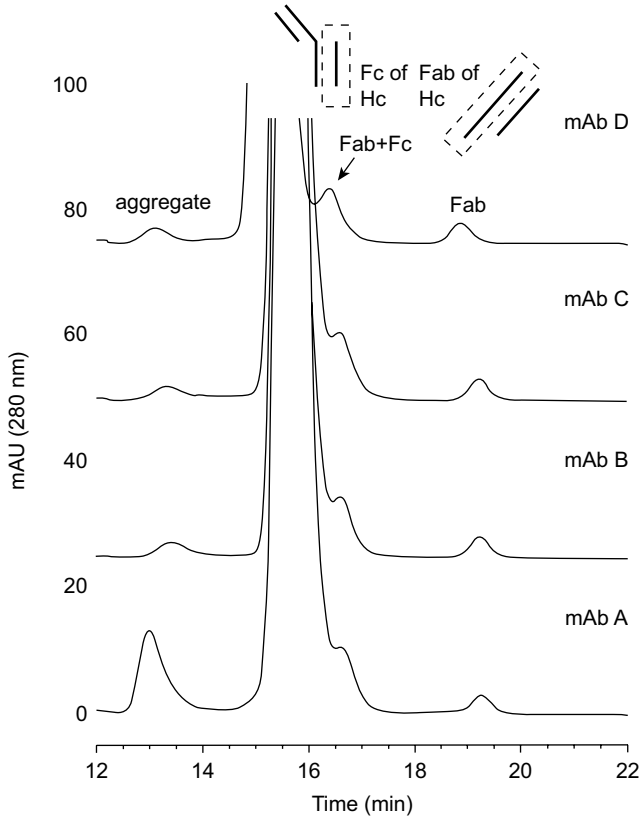

Figure 3.15 Size exclusion chromatography of four humanized IgG1 mAbs after incubation at pH 5.2 for 1 month at 40 °C.
From Cordoba et al. (2005).

An alternative mechanism may involve contaminating host cell proteases, which cleave at accelerated rates at higher temperature. Using a variety of protease inhibitors no change in fragmentation was detected at higher temperature suggesting that a nonenzymatic process was responsible for the fragmentation (Cordoba et al., 2005).

Another common fragmentation in mAbs occurs at the C-terminus of the heavy chains where C-terminus Lys and Arg residues are clipped. Examples include a chimeric IgG1 mAb (Harris, 1995), Herceptin® (Harris et al., 2001), and an anti-IgE mAb (Cacia et al., 1996). This particular degradation route generally occurs during the expression of the mAb in the host cell, usually Chinese hamster ovary (CHO) cells, and has been ascribed to carboxypeptidases from the host cell (Harris, 1995). Generally not all the mAb molecules have the C-terminal Lys or Arg removed, thus contributing to the heterogeneity of a mAb drug substance. This is not considered a safety or regulatory concern since plasma-derived proteins are often similarly processed.