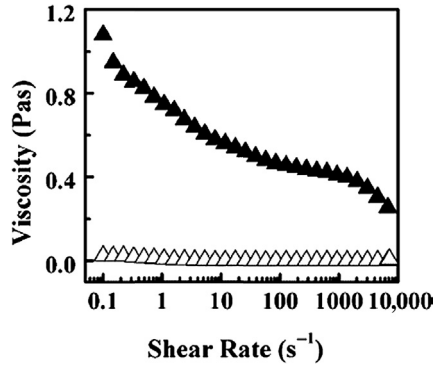

Figure 6.3 The non-Newtonian behavior of an IgG1 mAb as shown by dependence of viscosity on shear rate at 10 mg/mL (open triangles) and 200 mg/mL (solid triangles). All solutions were at 425 mM sucrose, 25 mM His, and 0.05% polysorbate 20 at pH 6. Viscosity was measured using an MCR300 rheometer (Anton PARR) equipped with a CP50-1 cone/plate measuring system at 25 °C. From Liu et al. (2005).

at higher shear (Figure 6.3) (Liu, Nguyen, Andya, & Shire, 2005) that yields a lower glide force. A model has been created for non-Newtonian fluids and used resulting in an excellent agreement with measured values for a Carbopol gel (Allmendinger et al., 2014). It has been suggested that the maximum force for manual injection with a syringe is about 30 N (Burckbuchler et al., 2010). Thus, injections for 1 mL in about 10 s become more difficult to handle at viscosity greater than 12 mPa s (Figure 6.2).

Impact on manufacturing of high-concentration SC formulations due to high viscosity

Creating a robust high-concentration formulation poses several challenges as discussed, but even if this is done successfully on a small scale a big challenge is to manufacture the formulation economically and in a reasonable time scale. The most commonly used unit operation in the pharmaceutical industry for concentration and exchange of the DS into the formulation is tangential flow filtration (Genovesi, 1983; van Reis & Zydney, 2001; Shiloach, Martin, & Moes, 1988). In this process, protein is circulated by pumping through a series of permeable hollow fiber tubes that allow for transport of water and small molecules, but not large macromolecules. Achieving a high concentration can be difficult because higher concentration than the target concentration can occur at the membrane interface, and depending on the mAbs propensity to interact with the solid surfaces of the fibers may result in adsorption and unfolding at the surface that leads to decreased transport and membrane fouling. Proteins can also be shear sensitive, and the continuous circulation through the pumps and tubing can result in shear or cavitation that results in protein denaturation and potential fouling of the tangential flow filtration (TFF) membranes. High viscosity of the protein solutions may result in high backpressures that may exceed the capacity