The relationship of concentration to aggregate and particulate formation will depend on the size of the aggregates as well as the mechanism for protein association (Glatz, 1992; Manning, Chou, Murphy, Payne, & Katayama, 2010; Manning, Patel, & Borchardt, 1989). It has been suggested that irreversible noncovalent aggregation may proceed via interaction of hydrophobic groups which is rate limiting, resulting in pseudo first-order reaction kinetics (Chi, Krishnan, Randolph, & Carpenter, 2003), rather than the expected higher order concentration dependency. However, at high concentrations, protein flexibility, alteration of volume required for a conformational change, and excluded volume effects may have considerable impact on the aggregation mechanism. Thus, even if there is a rate-limiting step that is concentration independent at lower concentrations, subsequent concentration-dependent steps may lead to more rapid kinetics at higher concentration. Although in general the rate of aggregation may increase with protein concentration there are exceptions such as aggregate formation at air–water interfaces, which as previously discussed has an inverse concentration dependency (Treuheit, Kosky, & Brems, 2002).

The reduced rate of commercial success in developing high-concentration SC formulations can put a severe strain on time and resources, and thus formulation scientists try to avoid huge developmental efforts leading to phase I clinical trials. Thus, many companies have used a platform approach, which may be successful if there is a large amount of experience in developing one class of molecule such as an IgG_1 mAb. This overall approach has been recently reviewed and may lead to faster development (Warne, 2011). However, one danger is that if the platform formulation does not work, valuable time will be lost when other formulations could have been explored.

Impact on delivery due to high viscosity at high mAb concentrations

In addition to the challenges in formulation, there are challenges in other areas required for successful pharmaceutical development of a high-concentration mAb formulation (Figure 1.1) such as the impact on delivery and ability to manufacture on a large scale. Macromolecules such as mAbs can be expected to have high viscosities at high concentration due to their size. Early studies on the concentration dependence of viscosity for an IgG_1 mAb showed a strong correlation with the time required to draw 1 mL through a syringe with a 27 gauge needle (Figure 6.1). The force required to inject a Newtonian fluid with viscosity η (Pa s) with a syringe of inner radius R_s equipped with a needle of length (l) and inner radius R_n at a volumetric flow rate Q (mL/s) is given by the Hagen–Poiseuille equation (Allmendinger et al., 2014; Sutera & Skalak, 1993):

$$F = (8QlR_s^2\eta)/R_n^4 + F_{friction} \tag{6.1}$$

The first term is the "glide" force required to push the fluid through the syringe and the added term is the frictional force that occurs from contact of the movable plunger with the inner barrel of the syringe. The frictional force can be determined by using glycerol–water solutions of known viscosity using (6.1) the Hagen–Poiseuille equation. Essentially a linear regression of a plot of the measured glide force as a function of viscosity gives the needle diameter, R_n if R_s is known, from the slope and the frictional force as the intercept.