(Andrade et al., 1992). However, not all proteins unfold on hydrophobic surfaces. It has been suggested that adsorption of mAbs to hydrophobic surfaces may not necessarily lead to an unfolding (Wiseman & Frank, 2012; Xu et al., 2006). This behavior is likely related to the type of surface and the conformational stability of a particular mAb. In situations where dilution of a mAb into an IV bag results in adsorption onto an IV bag surface without unfolding, there still is the possibility of under-dosing the patient due to loss of mAb.

Surfactants are added not just to prevent adsorption to solid surfaces but also to prevent interaction of the protein with the hydrophobic surface found at the air–water interface. As an example, for an IgG4 mAb formulated with suboptimal levels of the surfactant, polysorbate 20 (PS20) aggregates and subvisible particles were generated following gentle agitation after dilution into PVC and PO IV bags containing 0.9% saline (Kumru et al., 2012). The soluble aggregates and particulates were also characterized using HIAC particle counting, SEC, SDS PAGE, nanoparticle tracking analysis with a NanoSight LM-14 instrument, microflow digital imaging, and turbidity measurements. This study also showed that with sufficient PS20 particle formation was minimized. It was also shown that PVC IV bags caused more particle formation than the PO bags.

Clinical in-use studies as a strategy to address problems during IV administration of mAbs

Sreedhara et al. discussed the need for clinical in-use studies of IV bag preparations (Sreedhara et al., 2012). The pharmacist has the responsibility to ensure product stability in the final administered form and the setting of a "beyond-use" date based on the United States Pharmacopeia 797 where the "beyond-use" date is defined as the time the compounded sterile preparation must be used to avoid loss of potency, contamination, and safety risks. Since the manufacturer of the drug is most familiar with the drug products and has several assays used to support lot release and formulation development, it makes sense for the manufacturer to assess the "beyond-use" dating. In the published study by Sreedhara et al. four IgG1 mAbs were tested after dilution into IV bags (summarized in Table 5.1(a)). The impact of final PS20 concentration after dilution of mAb1 and mAb2 into PO IV bags with and without a 60 mL headspace showed that dilution of the PS20 resulted in aggregate formation for both mAbs after agitation in the presence of a headspace. The minimum level for protection was different for the two mAbs and no aggregate formed if the headspace was removed (Tables 5.1(b) and (c)). These results showed that dilution of the protective surfactant can lead to noticeable degradation of the product and that the generation of an air–water interface on agitation was responsible for the aggregate formation. This study shows the need for the manufacturer to conduct thorough "beyond-use" dating assessment, especially in regard to duration of storage, and impact of agitation and lowered surfactant levels due to dilution. There are several ways this problem can be mitigated. The choice of IV bag volume and levels of surfactant in the formulation can be adjusted so that there is a protective surfactant concentration after dilution into the IV bag. Also minimizing the headspace should work but it may be a less practical approach.