levels of these leachables within or between batches, even for the same manufacturer, can be significant (Desai et al., 2007; Nuijen et al., 2001). An extensive review on the compatibility, especially as to safety, has been published (Jenke, 2007). Zinc compounds that leach from plastic surfaces can generate particulates or precipitates of drug products (Ambados, 1996; Desai et al., 2007; Gallelli & Groves, 1993). Carcinogens, such as di-2-ethylhexyl-phthalate (DEHP), have also been identified as leachable compounds from the plastic used in IV bags (Nuijen et al., 2001). The two most widely used plastics in IV bags in the US are polyvinyl chloride (PVC) and polyolefin (PO). There are several reports documenting the presence of metals, cyclohexanone, DEHP, and other organic and acidic compounds due to leaching from PVC IV bag surfaces (Arbin, Jacobson, Hanniene, Hagman, & Ostelius, 1986; Borchert et al., 1986; Cheung, Hallock, Vishnuvajjala, Nguyenle, & Wang, 1998; Demore, Vigneron, Perrin, Hoffman, & Hoffman, 2002; Pearson & Trissel, 1993; Ulsaker & Korsnes, 1977). Manufacturers have claimed that PO bags and infusion sets are free of DEHP and other plasticizers, but other leachates such as organic acids and antioxidants have been reported (Jenke, 2005, 2007; Jenke et al., 2005; Labo, Tocchi, & Rock, 1984; Labow, Tocchi, & Rock, 1986). It has been shown in several cases that drugs diluted into PO bags are more stable than when diluted into PVC bags (Jenke, 2005; Jenke et al., 2005; Nuijen et al., 2001; Thiesen & Kramer, 1999).

As mentioned there can be variation of leachable levels between lot and within the same lot from the same manufacturer. This can complicate leachable IV bag studies requiring the testing of several bags from the same or different lots. Recently it was also shown that IV bags made from a particular polymer by the same manufacturer may contain components or methods of manufacture, which result in a different product that may have an impact on the quality of the pharmaceutical being prepared for IV administration (Chang et al., 2010). In this study, it was first shown that saline in PVC and PO bags from the same manufacturer had UV absorption spectra with a maximum absorption at ~320 nm which was not present in saline that never was in an IV bag (Figure 5.1(a)). Most strikingly, PO bags of different size (250 vs 100 mL) had different intensity of absorption where it was greater in the 100 mL size. It was also found that the absorbance increased with time of exposure in the 100 mL PO bags stored at 60 °C. A protein, dulanermin, normally a homotrimer, was found to dissociate after storage in 100 mL PO bags followed by freezing and thawing, but not in PVC bags (Figure 5.1(b)). Mass spectroscopy analysis identified the compound responsible as 2-mercaptobenzothiazole, and addition of pure 2-mercaptobenzothiazole to a solution of dulanermin after freeze–thaw resulted in the same degradation as what occurred in IV bags. At first glance, all of this was surprising since the 100 and 250 mL IV bags were made from the same plastic, PO, by the same manufacturer. Disassembly of the bags revealed that a rubber stopper was used at the entry port for the 100 mL size but not the 250 mL size (Figure 5.2). Incubation of this stopper with saline showed the presence of zinc as well as absorption spectra with a maximum at 320 nM. Thus, the source of the leachate was not from the PO resin but rather an additional rubber component at the entry port. This example illustrates the complexity and difficulty of performing leachate studies on IV bags used for IV administration and most importantly shows that leachates can impact the stability of the protein. In this example, a single Zn ion