

**Table 1** Usual Concentrations of Antioxidants and Chelating Agents

Antioxidant	Usual concentration
Acetylcysteine	0.5%
Ascorbic acid	0.02–1%
BHT, BHA, and propyl gallate	0.005–0.02%
Citric acid (chelator)	Variable*
Sodium edetate (chelator)	0.01–0.075
Sulfites	0.1–0.15%
Thioglycerol	0.1–1.0%
Thiourea	0.5–1.0
Tochopherols	0.05–0.075

\* Citric acid can be present in large amounts if it is present as a buffer (as well as present as a chelator).

Source: Table constructed from data published by Mendenhall (1984).

above, and at times they are detectable analytically. They are often oxidative in nature and metal ion catalyzed. Such a case in captopril (Lee and Notari, 1977).

Mendenhall (1984) has reviewed the stability aspects of parenteral products and has shown that discoloration is often either photochemical or oxidative. He has summarized the usually used antioxidants and chelating agents. These are shown in Table 1.

## 2.1. Swirly Precipitates

Often a parenteral solution will develop a swirly precipitate upon storage. This is most prevalent in vials and is usually an interaction with either the glass or the stopper. It may be difficult for the uninitiated to detect such slight changes, and the best person to use for this type of evaluation is a parenteral inspector. It is difficult to estimate the extent of the precipitate; it can be done by mechanical counting (e.g., with a Coulter counter), but the results are difficult to interpret. Often the count does not correspond to the "severity of the swirl." More to the point is how many swirls exist. If a box of e.g. 144 vials is placed on this type of stability, then the vials can be examined from time to time, and one may establish how many vials have become swirly. This number can then be treated in proper fashion to evaluate the severity of the problem, i.e., the stability parameter would be the number of swirly vials per box of 144.

Preferably there should be no swirls at all in the preparation, and if reformulation can be undertaken (which is wise), then an improved product would be the result. Otherwise, the stability program will establish the percentage probability of finding a vial with a swirl at the end of the expiration period. At times it is necessary to lyophilize products that are chemically stable, simply because the problem of swirls cannot be solved.

As mentioned, the occurrence of swirls is usually a container interaction, and a change in the stopper or the glass may often eliminate the problem. Vials should always be stored (a) upright, (b) on the side, and (c) upside down to check the interaction with the stopper. In this way primary evidence can be established as to the culpability of the closure.