in Europe have included calcium phosphate, MF-59 (a variation of biodegradable oil squalene), and other mineral oil emulsions or liposomes.

Buffering Agents

Physiologically tolerated buffers are added to maintain pH in a desired range and some examples include sodium phosphate, sodium bicarbonate, sodium citrate, and sodium acetate. The addition of a buffer is not absolutely necessary if it can be demonstrated that the formulation maintains the desired target pH range. In certain cases, these agents are present as a result of the process for achieving particle formation, yet have no significant buffering capacity at the pH of the final preparation. Ultralente insulin provides an example of such a situation. The sodium acetate is present during crystal growth at pH 5.5, but the final suspension is adjusted to neutral pH conditions where the buffering capacity is minimal. Potential interactions between buffers and metal ions must be considered as reaction products can lead to compromised stability.

Isotonicity Modifiers

These agents are added to minimize pain that can result from cell damage due to osmotic pressure differences at the injection depot. Glycerin and sodium chloride are examples used in insulin suspensions. Effective concentrations can be determined by osmometry using an assumed osmolality of 285 mOsmol/kg. Typical concentrations of 7 mg/mL and 16 mg/mL are used for sodium chloride and glycerin, respectively. Which agent is chosen may be dictated by the need to have a particular ingredient present during particle formation, as is the case for sodium chloride in the Lente insulin preparations. The two examples of isotonicity modifiers differ in ionic strength (sodium chloride: high ionic strength; glycerin: low ionic strength) and these properties might influence the choice of one over the other depending upon compatibility and stability considerations.

Preservatives (Antimicrobial Agents)

Multidose parenteral preparations require the addition of preservatives at sufficient concentration to minimize risk of patients becoming infected upon injection. Regulatory requirements for antimicrobial effectiveness have been established that take into account whether the formulation has inherent bacterial growth inhibition properties. Typical preservatives for parenteral suspensions include: m-cresol, phenol, methylparaben, ethylparaben, propylparaben, butylparaben, chlorobutanol, benzyl alcohol, phenylmercuric nitrate, thimerosol, sorbic acid, potassium sorbate, benzoic acid, chlorocresol, and benzalkonium chloride. Use of mercury-containing preservatives, especially for vaccine preparations, has been curtailed because of safety concerns. Indeed, toxicological issues will impose limitations on the use of other chemicals especially for chronic use applications.

It is well known that most vaccine suspensions contained organomercurial (thimerosal was most common) preservative agents for many years. However, there became an increasing awareness of the theoretical potential for neurotoxicity of even low levels of these organomercurials, especially in infants receiving multiple immunizations. The Food and Drug Administration worked with vaccine manufacturers to reduce or eliminate the inclusion of thimerosal from vaccine preparations. FDA websites (9) should be consulted for the latest discussions and decisions concerning preservative use in vaccine suspensions.

The type of preservative and concentration chosen may also be influenced by factors related to crystal growth, maintaining acceptable suspension stability, or compatibility with already grown crystals in addition to achieving necessary antimicrobial effectiveness. For example, insulin Ultralente cannot be formulated with phenol as the crystal morphology is destroyed over time (5), but methylparaben does not exhibit this effect. In contrast, insulin NPH crystals require phenolic preservative for crystal growth (10), and a mixture of m-cresol and phenol in a defined ratio is present in commercial preparations.

Stabilizers

Stabilizers include a variety of agents that impart stability to particles themselves or the entire suspension. General categories include: metal ions (zinc, calcium, etc.), salts used to produce