crystals, or organic molecules. Divalent metal ions play a pivotal role in insulin self-assembly and bringing about crystallization.

The various salts necessary to achieve crystal growth may also serve as stabilizers in the final suspension. Insulin Ultralente suspensions cleverly exploit the requirement for sodium chloride for crystal growth by also using the ingredient as a tonicity modifier. Organic ligands such as phenolic preservatives, in addition to serving a role as antimicrobial agents, may additionally function as stabilizers.

Complexing Agents

Protamine sulfate is an example of a complexing agent used to prepare suspensions. As excess protamine is undesirable from an immunogenicity standpoint and may impact the stability of biphasic (solution:suspension) mixtures by complexing some of the soluble component, the exact ratio required to completely complex all of the available peptide or protein needs to be determined. Under appropriate conditions, no detectable free protamine or peptide/protein remains in the supernatant.

Aluminum salts are complexing agents that were covered in the preceding text as adjuvants.

Wetting and Suspending Agents

Drugs in immediately acting injectable suspension formulations have limited aqueous solubility and do not easily "wet" because of their hydrophobicity. To enable these particles to be suspended in an aqueous vehicle, wetting agents such as surface-active agents, lecithin, or sorbitan trioleate are used to form an initial "slurry" of the insoluble particles prior to adding suspending agents. Basically wetting agents serve as dispersants to separate particles that otherwise would clump together and not easily separate to enable suspendability and dose homogeneity.

Suspending agents serve to maintain the insoluble particles in a suspended state for a period of time to allow for uniformity of dosage filled into each primary container and uniformity of dosage after each withdrawal of dose from the container. Suspending agents typically are polymers such as sodium carboxymethylcellulose (sodium CMC), polyvinylpyrrolidine (PVP), polyethylene glycol (PEG), or propylene glycol. Suspending agents may also be simple electrolytes such as sodium chloride. Suspending agents usually have an effect on increasing the viscosity of the vehicle although with injectable suspensions, viscosity cannot be too high or there will be problems with syringeability and injectability.

Other additives to injectable suspensions might include acids and bases such as hydrochloric acid and sodium hydroxide, necessary for pH adjustment during particle formation and of the final suspension.

It should be apparent to the pharmaceutical scientist involved in development of suspensions that the formulation and process are integrally related especially in the case of in situ particle growth and dose uniformity. Therefore, excipient selection must be considered with both formulation factors (stability, homogeneity, particle size, viscosity, tonicity, preservation, etc.) and processing factors (flowability, viscosity, dose uniformity, scale-up capability, etc.) in mind.

GENERAL REQUIREMENTS FOR SUSPENSION PRODUCTS

In addition to demonstrating appropriate chemical, physical, and microbiological stability over shelf life and during its intended in-use period, a well-formulated suspension should have the following characteristics:

1. Resuspension of particles is accomplished with reasonable agitation.
2. Rapid settling of dispersed particles does not occur.
3. Particles can be homogeneously dispersed such that consistent doses are obtained repeatedly.
4. The particles do not cake or pack at the bottom of the container over the shelf life period making it difficult to redisperse the product.