stoppering, and sealing of the product. So many injectable drugs are so unstable in solution that they must exist in the solid state so lyophilization processes and maintaining stability during lyophilization offer lots of challenges to the development scientist. Maintaining stability in the final container/closure system, while being stored, shipped, and manipulated prior to being administered to people or animals, all present enormous challenges that must be overcome.

Sterile dosage forms also have one extra requirement related to stability and that is maintaining sterility as a function of stability. So, with sterile dosage forms, product stability encompasses not only chemical and physical properties, but also includes microbiological stability (i.e., maintenance of sterility) throughout the shelf-life and usage of the product. Stability aspects of dosage forms are covered in chapters 8 through 11 and stability testing is discussed in chapter 24.

Compatibility

Most pharmaceutical dosage forms are consumed by patients without the patient or health care professional needing to do any manipulation with the dosage form prior to consuming it. While this is also true for many sterile dosage forms, there are also a significant number of sterile dosage forms that must be manipulated prior to injection. For example, freeze-dried products are released by the manufacturer, but must be manipulated by the user and/or health care professional prior to administration. The product must be reconstituted by sterile dilution, withdrawn into a syringe, and, often, then combined with another solution, perhaps a large volume infusion fluid, for administration. What all this means is that the sterile product must be shown to be compatible with diluents for reconstitution and diluents for infusion. Furthermore, many infusions contain more than one drug, so obviously the two or more drugs in the infusion system must be compatible.

Isotonicity

Biological cells maintain a certain "tone"; that is a certain biological concentration of ions, molecules, and aggregated species that give cells specific properties, the most important pharmaceutically of which is its osmotic pressure. Osmotic pressure is a characteristic of semipermeable cell membranes where osmotic pressure is the pressure where no water migrates across the membrane. Osmosis is the phenomenon where solutes will diffuse from regions of high concentration to regions of low concentration. So, if a formulation is injected that has an osmotic pressure less than that of biological cells, that is, the solution is hypotonic, the solvent from the injection will move across the cell membranes and could cause these cells to burst. If the cells are red blood cells, this bursting effect is called hemolysis. Conversely, if the formulation injected has an osmotic pressure greater than that of biological cells, that is, the solution is hypertonic, the solvent or water from the cell interior will move outside the cell membranes and could cause these cells to shrink, for example, crenation.

Ideally, any injected formulation should be isotonic with biological cells to avoid these potential problems of cells bursting or shrinking. Large-volume intravenous injections and small-volume injections by all routes other than the intravenous route must be isotonic to avoid major problems such as pain, tissue irritation, and more serious physiological reactions. Small-volume intravenous injections, while desirable to be isotonic, do not absolutely have to be isotonic because small volumes do not damage an excessive number of red cells that cannot be replaced readily.

It is well known that 0.9% sodium chloride solution and 5% dextrose solution are isotonic with biological cells. Why the difference in isotonic concentrations between these two common large-volume solutions? It has to do with the ability of the solute to dissociate into more than one species. Dextrose is a nonelectrolyte that in solution exists as a single entity; therefore, the osmotic pressure of a nonelectrolyte solution is proportional to the concentration of the solute. Sodium chloride is an electrolyte in solution that dissociates into two ionic species. Thus, the osmotic pressure of a solution containing an electrolyte dissociating into two species would be at least twice that of a solution containing a nonelectrolyte. The fact that the concentration of isotonic dextrose solution is over five times that of isotonic sodium chloride solution may be explained by the fact that ionic species attract solvent molecules, thus holding solvent molecules in solution and reducing their tendency to migrate across the cellular membrane. This, in turn, elevates osmotic pressure of the electrolytic solution such that a lower concentration of