5. Emulsions
6. Liquid concentrates ready for dilution prior to administration.

SUSTAINED RELEASE INJECTABLE DELIVERY SYSTEMS

An explosion of advances and commercial successes in controlling and/or sustaining the delivery of injectable drugs has occurred in the past few years (2–10). Major technologies developed for injectable controlled release include primarily microspheres, implants, or hydrogels. For pharmaceutical protein controlled or sustained release, microsphere or hydrogel technologies are the most likely choices. These systems include classical microcrystalline suspensions (e.g., NPH or Lente insulin formulations), biodegradable microspheres, nondegradable implants, gel systems, pegylated protein formulations, and hyperglycosylated protein formulations. Sustained- or controlled-release injectable delivery systems are desirable for three main reasons:

1. Increased duration of release, reduced number of injections, and increased compliance
2. Localized delivery in the case of cancer therapy and vaccinations
3. Protection against in vivo degradation of the active ingredient.

Polymeric Implants

Polymeric implants are sterile, solid drug products manufactured by compression, melting, or sintering processes. The implant consists of the drug and a biodegradable or replaceable polymeric system, with the polymeric system generally being the rate-controlling key to sustained and prolonged drug delivery. Commercial examples of polymeric implants include

1. Norplant®—Levonorgestrel in silastic capsules deposited subdermally into the upper part of the arm within one week of the onset of menses. Drug delivery can last up to five years.
2. Duros®—A titanium cylindrical osmotic pump implanted in the upper arm that delivers drug for weeks to months. Viadur® is an example.
3. Gliadel® wafer—Polifeprosan plus carmustine are formulated with a biodegradable polyanhydride copolymer with the wafer being 1.45 cm in diameter and 1 mm in thickness. This wafer is implanted into the cavity created by a brain tumor resection with up to eight wafers (61.6 mg carmustine) implanted that provides up to three weeks of antineoplastic therapy.
4. Compudose®—composed of silicone rubber for subcutaneous estradiol implantation behind the ear of cattle.

Polymeric implants are difficult to manufacture, drug stability sometimes is questionable, and surgical procedures are required to implant and remove the device.

Microspheres

Microspheres are injectable suspensions containing particles of diameters of 1 to 100 μm and are supplied as dried powders. Prior to injection, the particles are mixed with an appropriate vehicle, dispersed, and administered. Release kinetics are controlled by polymer degradation and diffusion of the drug, and the duration can be adjusted from days to months.

Microsphere encapsulation involves rather harsh conditions that may involve high shear, organic solvents, or high temperatures. In addition, the encapsulated molecules will be exposed to high body temperature over extended periods of time. As a result of these processing requirements and potential stability issues, the technology was not thought to be appropriate for peptides and proteins, but indeed there are several commercial examples of long-acting microspheres containing peptides and proteins. An example of a peptide that has been encapsulated is leuprolide acetate, a synthetic nonapeptide analog of LHRH (leutenizing hormone-releasing hormone). The microencapsulated peptide is marketed as Lupron® Depot and is used for the treatment of advanced prostatic cancer. Reconstitution of the dried particles with vehicle results in a suspension that is administered intramuscularly at monthly intervals.

Another example is microencapsulated human growth hormone. By exploiting the stabilizing effect of zinc ion complexation and using a low temperature method for incorporation during encapsulation, degradable microspheres are prepared containing structurally intact human growth hormone. Various formulations and manufacturing processes have been published although a primary preparation technique is the double emulsion solvent evaporation method.