MICROPRECIPITATION OF MICRO-NANOPARTICULATE PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention describes a chemical process of formulating micro-nanoparticulate pharmaceutical agent dispersions that have average particle diameters as small as 10 nm.

BACKGROUND OF THE INVENTION

Bioavailability is the degree to which a drug becomes available to the target tissue after administration. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/mL, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently, methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling, as discussed by Lachman, et al., *The Theory and Practice of Industrial Pharmacy,* Chapter 2, "Milling," p. 45, (1986), the limit of fineness is reached in the region of 100 microns (100,000 nm) when material cakes on the milling chamber. Lachnan, et al. note that wet grinding is beneficial in further reducing particle size, but that flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). However, there tends to be a bias in the pharmaceutical art against wet milling due to concerns associated with contamination. Commercial airjet milling techniques have provided particles ranging in average particle size from as low as about 1 to 50 μm (1,000–50,000 nm).

Other techniques for preparing pharmaceutical compositions include loading drugs into liposomes or polymers, e.g., during emulsion polymerization. However, such techniques have problems and limitations. For example, a lipid soluble drug is often required in preparing suitable liposomes. Further, unacceptable large amounts of the liposome or polymer are often required to prepare unit drug doses. Further still, techniques for preparing such pharmaceutical compositions tend to be complex. A principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomer or initiator, which can be toxic, at the end of the manufacturing process.

U.S. Pat. No. 4,540,602 (Motoyama, et al.) discloses a solid drug pulverized in a aqueous solution of a water-soluble high molecular weight substance using a wet grinding machine. However, Motoyama, et al. teach that as a result of such wet grinding, the drug is formed into finely divided particles ranging from 0.5 μm (500 nm) or less to 5 μm (5,000 nm) in diameter.

EPO 275,796 describes the production of colloidally dispersible systems comprising a substance in the form of spherical particles smaller than 500 nm. However, the method involves a precipitation effected by mixing a solution of the substance and a miscible non-solvent for the substance and results in the formation of non-crystalline nanoparticle. A somewhat more involved solvent shift method is described in U.S. Pat. No. 4,826,689 (Violanto) which produces uniform particles of drugs with diameters ranging between 0.5 to 1.0 μm. Furthermore, solvent precipitation techniques for preparing particles tend to provide particles contaminated with solvents. Such solvents are often toxic and can be very difficult, if not impossible, to adequately remove to pharmaceutically acceptable levels to be practical.

U.S. Pat. No. 4,107,288 describes particles in the size range from 10 to 1,000 nm containing a biologically or pharmaceutically active material. However, the particles comprise a crosslinked matrix of macromolecules having the active material supported on or incorporated into the matrix. Such polymeric material may accumulate in the body and cause toxic effects.

U.S. Pat. No. 4,725,442 (Haynes) describes water insoluble drug materials solubilized in an organic liquid and incorporated in microencapsules of phospholipids. However, the toxic effects of solubilizing organic liquids is difficult to overcome. Other methods of formation of pharmaceutical drug microencapsules include:

a) Micronizing a slightly-soluble drug by subjecting a mixture of the drug and a sugar or sugar alcohol to high-speed stirring comminution or impact comminution (EP 411,629A) together with suitable excipients or diluents. Such a method of encapsule formation does not lead to particle size as small as obtained by milling.

b) Polymerization of a monomer in the presence of the active drug material and a surfactant can lead to small-particle microencapsule (International Journal of Pharmaceutics, Vol. 52, pp. 101–108, 1989). This process, however, contains difficult-to-remove contaminants such as toxic monomers. Complete removal of such monomers can be expensive in manufacturing scales.

c) Co-dispersion of a drug or a pharmaceutical agent in water with droplets of carbohydrate polymer has been disclosed (U.S. Pat. No. 4,713,249 and WO-84/00294). The major disadvantage of the procedure is that in many cases, a solubilizing organic co-solvent is needed for the encapsulation procedure. Removal of traces of such harmful co-solvents can lead to expensive manufacturing processes.

Recently, many successful stable dispersions of nanoparticulate drug or pharmaceutical compositions have been prepared by wet milling of the agent in the presence of surfactants, polymers, block polymers, and oligomers as a mixture thereof as surface modifiers to produce sterically stabilized dispersions of nanoparticulates with particle diameters less than 400 nm (U.S. Pat. No. 5,145,684, WPI 87-200422/29, EP 0,498,482 A2). This wet milling procedure still leads to the incorporation of solubilized heavy metals from the attrition of the milling media, which in many cases must be removed from the dispersion by tedious ion exchange procedures to formulate the final pharmaceutical product. It is also well known that wet media milling procedures can not reduce average particle diameter to much less than 100 nm.

It is noted that filed concurrently herewith are a) EK Docket No. 71869 entitled, "Microprecipitation of Nanoparticulate Pharmaceutical Agents" by Pranab Bagchi et al; b) EK Docket 71870 entitled, "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal