

Agent Solution	
PCMPA #1	-20 g
n-propanol	-20 g
20% NaOH (aqueous)	-5 g

The above mixture was heated to 55° C. to dissolve then cooled to room temperature.

Surfactant Solution	
Distilled Water	-500 g
Aerosol A012 33% in water (BASF)	-14.3 g

Polystep B23 \Rightarrow $n\text{-C}_{12}\text{H}_{25}\text{-O-(CH}_2\text{-CH}_2\text{-O)}_{12}\text{-SO}_3\text{^{-N}a^+}$
(Stephen Chemicals)

The agent solution was added to the surfactant solution and then immediately neutralized with 60 g of 15% pro-
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nomic acid solution to form the micro-nanoparticulate pharmaceutical agent dispersion. The formed dispersion was continuously dialyzed against distilled water for 24 h and then concentrated by hanging the dispersion in the dialysis bag in a well ventilated hood for 7 days. The resultant dispersion was analyzed for PCMPA #1 concentration by HPLC and was found to be 14.2%. A cryo-transmission photoelectron micrograph of the dispersion particle is shown in FIG. 11. A PCS particle size distribution of the dispersion is shown in FIG. 12. In this distribution it is seen that 90% of particles lie between 7 and 12 nm with a Z-average particle size of 8 nm. From the micrograph of FIG. 10, it appears that the dispersion particles are fairly uniform, although very few particle as large as 35 nm diameter is observed.

Example 4

Lymphographic Imaging Using Micro-Nanoparticulate Dispersion of Example 2

A suspension prepared as described in Example 2 was used to image the lymph system (approximately 3 Kg rabbits) by computed tomography (CT). The suspension was dosed by percutaneous administration via the foot pads of the rabbits at 0.03 mL/Kg animal body weight and imaged 9 hours after administration. The CT images demonstrated enhanced X-ray contrast of the lymph nodes responsible for clearance from the anatomical areas of the rabbit injected with this formulation. Enhanced density was observed for times as long as 1 week after which the X-ray density of the lymph nodes returned to normal levels.

The invention has been described in detail with reference to preferred embodiments thereof, but it will be understood that various variations and modifications can be effected within the spirit and scope of the invention.

We claim:

1. A process of forming nanoparticulate dispersions of therapeutic pharmaceutical agents comprising:

first step of dissolution of the pharmaceutical agent in a liquid medium base in which said agent is poorly soluble and a non toxic solvent, miscible with the liquid medium,

a second step of adding to it an aqueous solution of one or more surface modifiers and a third step of neutralizing the formed alkaline solution with an acid to form a dispersion,

wherein, the pharmaceutical agent is formed by linkage between a photographic coupler molecule and a pharmaceutically useful chemical composition.

2. The process of claim 1 characterized by a dispersion having Z-average particle diameter less than 100 nm as measured by photon correlation spectroscopy.

3. The process of claim 1 wherein the base is selected from any one or a combination of the following:

NaOH

KOH

CsOH

trialkyl amines and

pyridine.

4. The process of claim 1 wherein the neutralizing acid is selected from:

a weak acid and

a strong acid.

5. The process of claim 1 wherein the neutralizing acid is selected from any one of the following:

HCl

HNO₃

HClO₄

H₂SO₄

formic acid

propionic acid

acetic acid and

butyric acid.

6. The process of claim 1 wherein the surface modifier is a mixture of surfactant selected from the following:

an anionic surfactant

a nonionic surfactant

a polymeric molecule and

an oligomeric molecule.

7. The process of claim 1 wherein the concentration of the dispersion is achieved by one of the methods selected from the following:

diafiltration

dialysis and

evaporation.

8. The process of claim 1 is characterized by the nanoparticulate dispersion having a Z-average particle diameter less than 50 nm as measured by photon correlation spectroscopy.

9. The process of claim 1 wherein the nanoparticulate pharmaceutical agent is concentrated to contain anywhere between 2 to 20% of the agent.

10. The process of claim 1 practiced in any mode selected from the following:

a batch process,

a semicontinuous batch process and

a continuous process.

11. The process of claim 1 wherein the water miscible solvent is selected from: methanol, ethanol, propanol, isopropanol, butanol and isobutanol acetone.

12. The process of claim 1 wherein step 3 is followed by step 4, the removal of salts and solvent by diafiltration or dialysis and step 5, concentrating to desired concentration of the agent dispersion.

13. A process of preparing an aqueous dispersion of a therapeutic pharmaceutical agent comprising:

continuously providing a first solution comprising water and surface modifier or a mixture thereof,

continuously providing a second solution comprising a pharmaceutical agent in aqueous base and a water miscible non toxic solvent to mix with the first flow, and