

dispersion of compound "X". The dispersion was then dialyzed against a continuous flow of distilled water for 24 h to remove the formed salts. The dialysis bag was then hung in a well ventilated hood for a week to concentrate the dispersion to contain about 10% of compound "X".

FIGS. 9a and 9b show the cryo-transmission photoelectron micrographs of particles of the two dispersions of Examples 1 and 2.

The dispersion of X-ray contrast agent "X" of Example 3 was prepared much in the same manner, except the contents of this various solution were as follows:

Agent solution:

compound "X"—12 g  
distilled water—12 g  
20% NaOH solution—27 g

The agent solution was dissolved at 75° C. and then cooled to room temperature.

Surfactant solution:

distilled water—300 g  
F-108 (BASF)—3.9 g  
surfactant "Y"—0.24 g  
20% NaOH solution—0.6 g

Acid solution:

15% ropronic acid—180 g

Using the above solutions and the method of FIG. 1 as before, the nanoparticulate dispersion of compound "X" of Example 3 was prepared. The dispersion was dialyzed continuously against distilled water in a dialysis tank and was concentrated to about 10% of compound "X" by hanging the dialysis bag in a well ventilated hood for seven days to evaporate the exuding water. FIG. 9c shows a cryo-transmission electron micrograph of the formed particles.

The particle size distributions of all the dispersions of Examples 1, 2, and 3 are shown in FIGS. 10a, 10b, and 10c, respectively as determined by PCS. It is observed in FIG. 10 that the major peak of the distribution of all these dispersions lie around 250 nm in diameter. The Z-average particle size of the three dispersions determined by photon correlation spectroscopy (PCS) and are shown in Table I. The dispersions were subjected to an autoclave treatment at 120° C. for 25 min to determine effect of sterilization. After autoclaving, the Z-average particle diameters were also determined and are also shown in Table I.

TABLE I

Example	Surface Modifying Surfactants	PCS Particle Diameter, Z-Av. nm	
		Initial	After Autoclaving
1	T-908 + Y	227	368
2	T-908 + Y	235	390
3	F-108 + Y	253	284

It is seen in Table I that all the dispersions seem to be substantially stable to autoclave treatment exhibiting only small growth of particle diameter. Even after autoclaving the particle size of all the dispersions remain less than 400 nm in diameter.

Lymphographic imaging using nanoparticulate compound "x" was achieved as follows:

The suspension of Example 3 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 h 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 microprecipitation process of forming nanoparticulate dispersions of pharmaceutical agents comprising:

a first step of dissolution of the pharmaceutical agent in aqueous base,

a second step of adding to step a an aqueous solution of slightly alkaline mixture of at least one nonionic surface active surface modifier and at least one anionic surface active surface modifier and

a third step of neutralizing the formed alkaline solution with an acid to form a dispersion,

wherein the said anionic surface active surface modifier is structurally on a molecular basis at least 75% identical to the chemical structure of the pharmaceutical agent.

2. The process of claim 1 wherein the pharmaceutical agent is selected from:

therapeutic agent and  
diagnostic agent.

3. The process of claim 1 wherein the nanoparticulate dispersion is characterized by a Z-average particle diameter less than 400 nm as measured by photon correlation spectroscopy.

4. 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.

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

a weak acid and  
a strong acid.

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

HCl  
HNO<sub>3</sub>  
HClO<sub>4</sub>  
H<sub>2</sub>SO<sub>4</sub>

formic acid  
propionic acid  
acetic acid and  
butyric acid.

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

an anionic surfactant  
a nonionic surfactant  
a polymeric molecule and  
an oligomeric molecule.