IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Neil P. DESAI et al.

Application No.: 11/520,479 Confirmation No.: 8972

Filed: September 12, 2006 Art Unit: 1611

For: NOVEL FORMULATIONS OF PHARMACOLOGICAL AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF

Examiner: T. Love

SUPPLEMENTAL DECLARATION OF NEIL P. DESAI PURSUANT TO 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

I, Neil P. Desai, declare as follows:

1. This declaration is in addition and supplemental to the 37 C.F.R. §1.132 declaration ("the Previous Declaration") previously submitted to the Patent Office on January 27, 2012.

2. I have reviewed the Office Action dated May 2, 2013. I understand that claims in the above-captioned patent application remain rejected as being obvious over one of Abraxis' earlier patents, U.S. Pat. No. 5,439,686 ("Desai"), for which I am also a named inventor, in view of U.S. Pat. No. 5,407,683 ("Shively"). In this supplemental declaration, I provide more information about the data presented in the Previous Declaration as well as the cited reference Desai.

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3. In the Previous Declaration, I presented, in part, experimental data showing the advantageous properties of the nanoparticle formulations recited in the claims of the above-captioned patent application ("the '479 application"). The experiment compared the physical stability of two pharmaceutical formulations (Composition 1 and Composition 2) containing nanoparticles comprising a solid core of paclitaxel and an albumin coating at a paclitaxel concentration of 5 mg/ml.

4. As discussed in the Previous Declaration, upon storage at 40 °C for 24 hours,[1] there was a distinctly visible sediment layer at the bottom of the vials containing Lot 1 and Lot 2 of Composition 2 indicating instability of Composition 2. Exhibit 1; *See also* Exhibit 3 of the Previous Declaration. Such sedimentation was not observed in the vial containing Composition 1. Microscopic observation of the formulations stored at 40 °C for 24 hours at 400x magnification revealed large particles in Composition 2 indicating particle growth and aggregation, which were not observed in Composition 1. Exhibit 2; *See also* Exhibit 4 of the Previous Declaration.

5. Further, as discussed in the Previous Declaration, upon storage at 40°C for 24 hours, the weight mean diameter of the nanoparticles in Composition 1 remained unchanged. In Composition 2, by contrast, the weight mean diameter of the nanoparticles increased significantly upon storage demonstrating instability of Composition 2. Exhibit 3; *See also* Table 1 of the Previous Declaration.

6. The table below summarizes and provides additional particle size characteristics of the two different formulations tested in the experiment.[2]

Formulation	Weight Mean Diameter, nm	95% Weight Distribution (D_{95}), nm	99% Weight Distribution (D_{99}), nm
Composition 1	140	240	282
Composition 2, Lot 1	245	500	633
Composition 2, Lot 2	228	496	638

[1] Storage at 40 °C for 24 hours is equivalent to storage at room temperature for at least three days.
[2] Particle size was determined by disc centrifugation method immediately after reconstitution of the formulations at about 5 mg/ml. Size may differ slightly when using a different measurement method such as dynamic light scattering.

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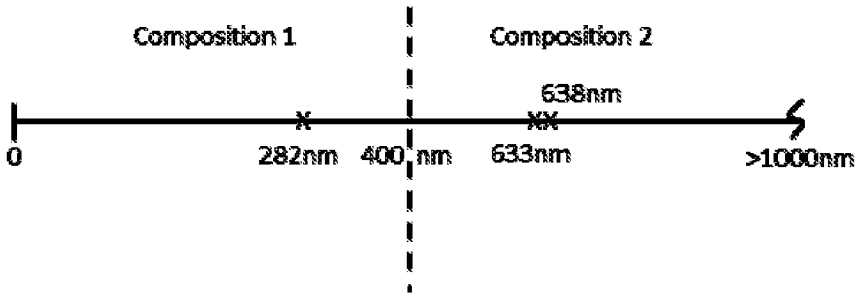
The 95% and 99% weight distribution in the table above provides the size in nanometers below which 95% and 99% by weight of the particles lie, respectively. For example, in Composition 1, 95% of the particles in the formulation have a particle size below 240 nm. In Composition 2, 95% of the particles in the formulation have a particle size below 500 (Lot 1) and 496 nm (Lot 2). In Composition 1, there was no detectable percentage of nanoparticles that have a size above 400 nm, with 99% of the particles lying below 282 nm. In Composition 2, by contrast, at least 10% of the nanoparticles in the formulation had a particle size that was above 400 nm, with 99% of the particles lying below 633 (Lot 1) and 638 nm (Lot 2).

7. The diagram below further illustrates the 99% weight distribution of the two different formulations.



8. Notably, both Composition 1 and Composition 2 are albumin-coated paclitaxel nanoparticle formulations having a particle size below 1000 nm, yet they behave differently in stability assays. Composition 1, which contains no detectable percentage of nanoparticles that have a size above 400 nm, was shown to be stable at paclitaxel concentration of 5 mg/ml. By contrast, Composition 2, which contains nanoparticles slightly greater than 400 nm, was unstable at the same paclitaxel concentration under the same conditions. This result was unexpected.

9. As discussed in the Previous Declaration, physical stability is a key consideration for ensuring safety and efficacy of nanoparticle drug products. The tendency of nanoparticles to precipitate and/or increase in size (for example by aggregation) increases as the drug concentration increases. For example, an increase in drug concentration in a nanoparticle formulation can result in

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an increase in particle concentration, namely, the number of particles per unit volume. An increase in particle concentration in turn would increase the frequency of collision of the particles and thus increase the tendency of the particles to aggregate and become unstable. This is demonstrated in Burns et al., Langmuir 1997, 13, 6413-6420 (Exhibit 4), for example, which examined particle aggregation in various formulations having different particle concentrations. The authors concluded that "[a]s the particle concentration is increased, the aggregate growth is more rapid, most likely due to the increased collision frequency." *See also* Kallay et al., J. Colloid and Interface Science 253, 70-76 (2002) (Exhibit 5) at page 75 ("the aggregation rate is proportional to the square of the particle concentration….").

10. The estimated particle concentration for Composition 1 discussed above, namely, the albumin-coated solid paclitaxel nanoparticle formulation having a particle size less than 400 nm at paclitaxel concentration of 5 mg/ml, is about 8.0×10^{13}/ml.[3] The stability of such a formulation at 5 mg/ml or higher was unexpected based on the high particle concentration.

11. The stability of albumin-coated paclitaxel nanoparticle formulation having particle size less than 400 nm is in stark contrast with that of a different non-albumin based paclitaxel nanoparticle formulation having particle size less than 400 nm. In a study conducted to compare the physicochemical characteristics and stability of two different commercially-approved nanoparticle formulations of paclitaxel, namely, Abraxane® (an albumin-coated solid paclitaxel nanoparticle formulation having particle size less than 400 nm, similar to Composition 1 described above) and Genexol-PM ® (a non-albumin polymeric-micelle formulation of paclitaxel having particle size less than 400 nm), only Abraxane® was shown to be stable at 40 °C over 24 hours at paclitaxel concentration of 5 mg/ml while the Genexol-PM ® formulation showed excessive precipitation under these conditions. Ron et al., 99th AACR Annual Meeting Abstract, No. 5622 (Exhibit 6). This study further illustrates the difficulty and challenge in obtaining paclitaxel nanoparticle formulations having

[3] The particle concentration is estimated with the assumption that the average particle size of the particles in the formulation is about 140 nm and the particle density is about 1165 kg/m^3.

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particle size less than 400 nm that are stable at paclitaxel concentration of 5 mg/ml or higher, and the unexpected stability of the claimed albumin-coated solid nanoparticle formulation.

12. Thus, albumin-coated paclitaxel nanoparticle formulations having particle size less than 400 nm were stable at 5 mg/ml. This is in stark contrast with an albumin-coated paclitaxel nanoparticle formulation which contains particles slightly greater than 400 nm, and a non-albumin based paclitaxel nanoparticle formulation having particle size less than 400 nm, both shown to be unstable under the same conditions at paclitaxel concentration of 5 mg/ml. These results demonstrate the advantageous and unexpected stability of the albumin-coated paclitaxel nanoparticle formulation recited in the claims of the '479 application, especially in view of the high particle concentration in such a formulation and the well-known principle that the aggregation rate of nanoparticles is proportional to the square of the particle concentration.

13. The Examiner cites Desai as allegedly teaching a stable albumin-coated nanoparticle formulation. As discussed in the Previous Declaration, Example 5 of Desai, which the Examiner relies on as teaching stability of albumin-coated nanoparticle formulations, refers to the stability of polymeric shells containing buoyant soybean oil with density less than water. No drug was present within the polymeric shell. The stability of the "drugless" oil-containing polymeric shells discussed in Example 5 of Desai thus provides no suggestion that a nanoparticle formulation comprising a solid core of paclitaxel and an albumin coating would be stable at paclitaxel concentration of between 5-15 mg/ml. Furthermore, as discussed in the Previous Declaration, an increase in loading of paclitaxel within the polymeric shells as taught in Example 4 of Desai would be expected to increase the particle size and/or density of the particles, which in turn could increase the tendency of the particles to precipitate.

14. Although a separate example in Desai, Example 9, teaches preparation of polymeric shells containing a solid core of pharmaceutically active agent such as paclitaxel, there is no information about the concentration of the paclitaxel in such polymeric shell formulation. Nor is there any indication that the particles in such polymeric shell formulation are smaller than 400 nm.

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