CLAIMS

1. A method for quantitative measurement of particle interior content using imaging, comprising the following steps:

(a) providing a sample (100) of virus-like particles (VLPs) or virus particles;

(b) preparing the sample to maintain the sample (100) in a native unstained hydrated state;

(c) acquiring images of the sample in the native unstained hydrated state;

(d) observing the particle interior content of each VLP or virus particle in the images;

(e) based on the observation of the particle interior content, measuring an intensity of the particle interior content;

(f) based on the measured intensity, determining an amount of the particle interior content to assess whether the VLPs or virus particles are empty (104), filled (102) or ambiguous (106).

2. The method according to claim 1 wherein the method comprises after step (c), an additional step of automatically or manually detecting particles in the images, and deleting particles that are smaller than a lower size limit and larger than an upper size limit from the images.

3. The method according to claim 1 wherein step (f) involves the following:

a particle that has an inner density with no distinct boundary between a particle shell and a particle core is classified as a filled particle;

a particle that has a distinct outer shell and a minute internal density is classified as an empty particle; and

a particle that displays characteristics of both a filled particle and an empty particle is classified as an ambiguous article.

4. The method according to claim 1 wherein:

a sample (100) of virus-like particles (VLPs) is provided in step (a); and

Cryo Transmission Electron Microscopy is used to determine particle interior content of the VLPs in step (f).

5. The method according to claim 1 wherein:

a sample (100) of adeno associated virus (AAV) particles is provided in step (a); and

step (f) involves determining the particle interior content of the AAV particles.

6. The method according to claim 5 wherein step (f) involves the following:

an AAV particle that contains a gene is classified as a filled particle (102);

an AAV particle that contains no gene is classified as an empty particle (104); and

an AAV particle that displays characteristics of both a filled particle and an empty particle is classified as an ambiguous article.

7. The method according to claim 1 wherein:

a sample (100) of VLPs is provided in step (a); and

step (b) involves adding an ionic liquid to the sample to keep the VLPs in a hydrated state.

8. The method according to claim 1 wherein step (b) involves imaging the sample in a hydrated liquid state by using a liquid sample holder.