APPARATUS FOR RESOLVING IMAGING PROBLEMS CAUSED BY THE MENISCUS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] Priority is claimed to U.S. Provisional Patent Application No. 62/781,797, filed December 19, 2018, the entire contents of which are hereby incorporated herein by reference.

FIELD OF DISCLOSURE

[0002] The present application relates to techniques for imaging wells or other vessels containing fluid samples.

BACKGROUND

[0003] In certain contexts, such as cell line monitoring or quality control procedures for manufactured drug products, it is necessary to examine fluid samples. For example, it may be necessary to identify and/or characterize particles (e.g., cells, debris, etc.) in a fluid. A common way of inspecting such samples is to inject the samples into wells of a well plate, after which an automated system shifts the well plate such that each of the wells is sequentially aligned with the optical path of an imager. As each well is aligned with the optical path, the imager captures one or more images of the well. The well images may then be stored and analyzed by a human analyst, and/or by a computer.

[0004] To ensure a robust inspection, the well images must maintain a certain level of quality (e.g., resolution, focus, etc.). However, various factors can make this challenging, such as well wall shadows and limitations on the resolution of the imager. One cause of sub-optimal images is the meniscus (upper curved surface) that forms due to the intermolecular attraction between the fluid and the well walls. Due to the small diameter of the typical well, the meniscus can significantly distort the well image. FIG. 1A provides an illustration, with a well 100 containing a fluid sample 102 that forms a meniscus 104. Well 100 typically has a transparent bottom, allowing incident light 106 from an illumination source to pass through both fluid sample 102 and well 100, after which an imager (e.g., a charge-coupled device (CCD) camera) captures an image of fluid sample 102. As seen in FIG. 1A, the curvature of meniscus 104 causes incident light 106 to refract at an angle that increases with proximity to the wall of well 100. This refraction degrades the phase contrast, which in turns reduces the image quality.

[0005] Several techniques for resolving the problems created by the meniscus have been proposed. For example, an imaging system may compensate for the meniscus refraction by using a lens that distributes light on the sample in a non-uniform manner. One such example is shown in FIG. 1B, where a lens 120 is used to compensate for the refraction of incident light 106 by meniscus 104. As seen in FIG. 1B, however, this technique can result in a failure to image an annular portion 122 of well 100 near the perimeter. Annular portion 122 can be large enough that, in some applications, the failure to image portion 122 is unacceptable. An alternative proposal is shown in FIG. 1C, where an element 130 (e.g., of a well plate "cover") with a flat surface 132 is inserted into well 100 and fluid sample 102. As seen in FIG. 1D, however, this may result in an air bubble 140 being trapped between flat surface 132 and fluid sample 102. Air bubbles of this sort can distort the well image in a manner for which it is very difficult to compensate, e.g., due to the variable position, size and shape of bubbles. While some rounding of the edges of the flat surface has been suggested, the large flat area still allows bubbles to be trapped in a significant number of samples. Thus, there is a need for an apparatus or technique that resolves the imaging problems created by the meniscus, while still permitting imaging of substantially the entire well, and without introducing (or at least, making less likely) air bubbles that may distort the well image.

SUMMARY

[0005a] According to a first aspect of the present invention, there is provided a well plate cover comprising: a base defining a base plane; and a plurality of insertion elements, wherein at least a portion of each of the insertion elements is transparent, each of the insertion elements (i) is coupled to the base, and (iii) extends, in a direction orthogonal to the base plane, from the base to

a distal end surface of the insertion element, the distal end surface of each of the insertion elements includes an apex that, when the respective insertion element is inserted into a well of a well plate, extends further into the well than any other portion of the distal end surface, and the apex is ~~(i) an apex point, (ii) an apex line, or (iii)~~ an apex plane~~, the apex plane~~ having a diameter that is less than one half of a maximum diameter of the distal end surface~~.~~; the apex plane of each of the distal end surfaces forms a circle; and the distal end surface of each of the insertion elements includes a plurality of planar tiers forming concentric rings around the respective apex plane and sized to fit into the well, with each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the base than is the previous planar tier.

[0005b] According to a second aspect of the present invention, there is provided a method for imaging a fluid sample in a vessel, the method comprising: inserting at least a distal end surface of an insertion element into the fluid sample in the vessel, wherein at least a portion of the insertion element is transparent, wherein the distal end surface includes an apex that extends further into the vessel than any other portion of the distal end surface, and wherein the apex is ~~(i) an apex point, (ii) an apex line, or (iii)~~ an apex plane~~, the apex plane~~ having a diameter that is less than one half of a maximum diameter of the distal end surface; wherein: the apex plane forms a circle; the insertion element includes a proximal end opposite the distal end surface; the distal end surface includes a plurality of planar tiers forming concentric rings around the apex plane and sized to fit into the well; and each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the proximal end of the insertion element than is the previous planar tier; positioning the vessel in an optical path of an imager; illuminating the vessel while the insertion element is inserted into the fluid sample in the vessel; and capturing, by the imager, an image of the illuminated vessel while the insertion element is inserted into the fluid sample in the vessel.

[0006] Embodiments described herein relate to systems and methods that improve upon conventional techniques for imaging fluid-filled vessels by resolving certain problems relating to the fluid meniscus. For a given vessel, an insertion element is inserted into the fluid within the vessel. The insertion element may be wholly transparent, or may only be transparent in certain

What is claimed is:

1. A well plate cover comprising:

a base defining a base plane; and

a plurality of insertion elements, wherein

at least a portion of each of the insertion elements is transparent,

each of the insertion elements (i) is coupled to the base, and (iii) extends, in a direction orthogonal to the base plane, from the base to a distal end surface of the insertion element,

the distal end surface of each of the insertion elements includes an apex that, when the respective insertion element is inserted into a well of a well plate, extends further into the well than any other portion of the distal end surface, and

the apex is ~~(i) an apex point, (ii) an apex line, or (iii)~~ an apex plane~~, the apex plane~~ having a diameter that is less than one half of a maximum diameter of the distal end surface~~.~~;

the apex plane of each of the distal end surfaces forms a circle; and

the distal end surface of each of the insertion elements includes a plurality of planar tiers forming concentric rings around the respective apex plane and sized to fit into the well, with each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the base than is the previous planar tier.

2. The well plate cover of claim 1, wherein ~~the apex~~ at least a portion of each insertion element is at least one of coated and treated with a hydrophilic surface ~~an apex point~~.

~~3. The well plate cover of claim 2, wherein the distal end surface of each of the insertion elements forms a cone or a pyramid.~~

~~4. The well plate cover of claim 2 or 3, wherein the apex point of each of the distal end surfaces is located at a center of the distal end surface.~~

~~5. The well plate cover of claim 2, wherein the apex point of each of the distal end surfaces is located at a position along a perimeter of the distal end surface.~~

~~6. The well plate cover of claim 1, wherein the apex of each insertion element is an apex line.~~

~~7. The well plate cover of claim 6, wherein the apex line of each of the distal end surfaces divides the distal end surface into two parts of equal size.~~

~~8. The well plate cover of claim 1, wherein the apex of each insertion element is an apex plane.~~

~~9. The well plate cover of claim 8, wherein the apex plane of each of the distal end surfaces forms a circle.~~

~~10. The well plate cover of claim 9, wherein the distal end surface of each of the insertion elements includes a plurality of planar tiers forming concentric rings around the respective apex plane, with each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the base than is the previous planar tier.~~

~~11~~3. A method for imaging a fluid sample in a vessel, the method comprising:

inserting at least a distal end surface of an insertion element into the fluid sample in the vessel,

wherein at least a portion of the insertion element is transparent,

wherein the distal end surface includes an apex that extends further into the vessel than any other portion of the distal end surface, and

wherein the apex is ~~(i) an apex point, (ii) an apex line, or (iii)~~ an apex plane~~, the apex plane~~ having a diameter that is less than one half of a maximum diameter of the distal end surface;

wherein:

the apex plane forms a circle;

the insertion element includes a proximal end opposite the distal end surface;

the distal end surface includes a plurality of planar tiers forming concentric rings around the apex plane and sized to fit into the well; and

each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the proximal end of the insertion element than is the previous planar tier;

positioning the vessel in an optical path of an imager;

illuminating the vessel while the insertion element is inserted into the fluid sample in the vessel; and

capturing, by the imager, an image of the illuminated vessel while the insertion element is inserted into the fluid sample in the vessel.

~~12~~4. The method of claim ~~11~~3, wherein ~~the apex is an apex point~~ at least a portion of each insertion element is at least on of coated and treated with a hydrophilic surface.

~~13. The method of claim 12, wherein the distal end surface forms a cone or a pyramid.~~

~~14. The method of claim 12 or 13, wherein the apex point is located at a center of the distal end surface.~~

~~15. The method of claim 11, wherein the apex is an apex line.~~

~~16. The method of claim 15, wherein the apex line divides the distal end surface into two parts of equal size.~~

~~17. The method of claim 11, wherein the apex is an apex plane.~~

~~18. The method of claim 17, wherein the apex plane forms a circle.~~

~~19. The method of claim 18, wherein:~~

~~the insertion element includes a proximal end opposite the distal end surface;~~

~~the distal end surface includes a plurality of planar tiers forming concentric rings around the apex plane; and~~

~~each successive planar tier, when progressing outwardly from the apex plane towards a perimeter of the distal end surface, is closer to the proximal end of the insertion element than is the previous planar tier.~~

~~20~~5. The method of any one of claims ~~11-19~~3 or 4, wherein:

the distal end surface includes a sloped portion positioned between the apex and a perimeter of the distal end surface; and

illuminating the vessel includes directing light so as to compensate for light refraction caused by the sloped portion of the distal end surface.