into sensitive species that are sprayed separately to give a layered granule; wherein the reactive species are components that easily react with other components in the media or feed, thereby producing adducts, cross-linked products or precipitates; and wherein the sensitive species are components that may be destroyed by unwanted reaction with reactive species.

[0002c] In another aspect, the present disclosure refers to a layered base particle or a layered base granule comprising in its core a mixture of sensitive components, anti-oxidant components, and neutral components, wherein said sensitive components, anti-oxidant components, and neutral components are layered one by one on top of each other, and wherein said sensitive components or said neutral components or said anti-oxidant components form the central core of the layered base granule, wherein the sensitive components are components that may be destroyed by unwanted reaction with reactive species.

[0002d] In yet another aspect, the present disclosure refers to a method of culturing a cell in a liquid reconstituted from the layered base particle or layered base granule as disclosed herein, comprising: i) reconstituting the layered base particle or layered base granule in a suitable liquid or buffer; wherein said layered base particle or layered base granule is a cell culture medium, feed, supplement or concentrate; ii) culturing the cell is the reconstituted liquid under conditions favorable for the growth of the cell.

[0002e] In yet another aspect, the present disclosure refers to a kit comprising: i) a first container comprising a layered base particle or a layered base granule as disclosed herein; wherein said layered base particle or said layered base granule is a cell culture medium, feed, supplement or concentrate; ii) instructions for using the layered base particle or the layered base granule for cell culture.

[0003] In one example, the disclosure is directed in part to methods of making a media or a feed composition for culturing cells, comprising: i) subjecting a dry powder to suspension in a moving column of a gas in a fluid bed apparatus; ii) introducing at least one solvent using a sprayer into the dry powder of step (i) to form a layered base particle; and iii) drying the layered base particle.

[0004] In another example, the disclosure is also directed in part to methods of making a media or a feed composition for culturing cells, comprising: i) subjecting a dry powder to suspension in a moving column of a gas in a fluid bed apparatus; ii) introducing a first solvent using a first sprayer onto

the dry powder of step (i) to form a base granule; iii) introducing at least one second solvent using a second sprayer onto the base granule of step (ii) to form a layered base granule; iv) drying the layered base granule.

[0005] Also disclosed is that the dry powder may be a basal media powder, a complete media powder, a cell culture feed, a cell culture supplement, a cell culture media or feed concentrate or an amino acid mixture.

[0006] Also disclosed is that the first sprayer may be selected from the group consisting of: a top sprayer, a bottom sprayer and a tangential sprayer. Alternately, the first or the second sprayer may be selected from

the group consisting of: a top sprayer, a bottom sprayer and a tangential sprayer. In a preferred example, the second sprayer may be a bottom sprayer.

[0007] Also disclosed is that the second sprayer may spray a plurality of solvents on to the base granule to form a multilayered base granule or multilayered base particle respectively. Alternately, the second sprayer may spray the plurality of solvents sequentially, such that there are intermittent drying steps between each spraying step. And alternately, the second sprayer may spray the plurality of solvents sequentially without any intermittent drying steps between each spraying step.

[0008] Also disclosed is that each solvent in the plurality of solvents may have one component; or, the same components; or, each solvent may have different components. For example, each solvent may have a mixture of components. Also disclosed is that the solvent comprises a reactive species. Also disclosed is that the solvent comprises a sensitive species.

[0009] Also disclosed is that the components to be sprayed through the solvent are segregated into reactive species and into sensitive species.

[0010] Also disclosed is that the reactive species and the sensitive species are sprayed separately to give a layered granule. Also disclosed is that the reactive species may be selected from the group consisting of one or more trace elements, one or more reactive amino acids, one or more reactive amino acids, one or more metal salts, one or more acid soluble reactive groups, one or more alcohol soluble reactive groups and one or more pH modifier groups.

[0011] Also disclosed is that the sensitive species may be selected from the group consisting of one or more polyamines, one or more vitamins, one or more growth factor and one or more labile amino acids.

[0012] Also disclosed is that an inlet gas is used in the methods which may be at about temperature 20° C to 30° C. Also disclosed is that the inlet gas used in the method may be at about temperature 25° C.

[0013] Also disclosed is that the vitamins that may be sensitive are selected from the group consisting of: vitamin B12, biotin, choline, folic acid, niacinamide, pyridoxine, riboflavin, thiamine, ascorbic acid and para-aminobenzoic acid (PABA).

[0014] Also disclosed is that the drying step may be at about temperature 50° C to 60° C.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of making a media or a feed composition for culturing cells, comprising:

i) subjecting a dry powder to suspension in a moving column of a gas in a fluid bed apparatus;

ii) introducing at least one solvent using a sprayer into the dry powder of step (i) to form a layered base particle;

iii) drying the layered base particle, wherein each solvent has a mixture of components and wherein the components are segregated into reactive species and into sensitive species that are sprayed separately to give a layered granule;

wherein the reactive species are components that easily react with other components in the media or feed, thereby producing adducts, cross-linked products or precipitates; and

wherein the sensitive species are components that may be destroyed by unwanted reaction with reactive species.

2. A method of making a media or a feed composition for culturing cells, comprising:

i) subjecting a dry powder to suspension in a moving column of a gas in a fluid bed apparatus;

ii) introducing a first solvent using a first sprayer onto the dry powder of step (i) to form a base granule;

iii) introducing at least one second solvent using a second sprayer onto the base granule of step (ii) to form a layered base granule;

iv) drying the layered base granule, wherein each solvent has a mixture of components and wherein the components are segregated into reactive species and into sensitive species that are sprayed separately to give a layered granule;

wherein the reactive species are components that easily react with other components in the media or feed, thereby producing adducts, cross-linked products or precipitates; and

wherein the sensitive species are components that may be destroyed by unwanted reaction with reactive species.

3. The method of making the media or the feed composition for culturing cells of claim 1 or 2, wherein the dry powder is a basal media powder, a complete media powder, a cell culture feed, a cell culture supplement, a cell culture media or feed concentrate or an amino acid mixture.

4. The method of making the media or the feed composition for culturing cells of claim 1, wherein the first sprayer is selected from the group consisting of: a top sprayer, a bottom sprayer and a tangential sprayer.

5. The method of making the media or the feed composition for culturing cells of claim 2 or 3, wherein the first or the second sprayer is selected from the group consisting of: a top sprayer, a bottom sprayer and a tangential sprayer.

6. The method of making the media or the feed composition for culturing cells of claim 2 or 3 or 5, wherein the second sprayer is a bottom sprayer.

7. The method of making the media or the feed composition for culturing cells of any of claims 2 to 3 and claims5 to 6, wherein the second sprayer sprays a plurality of solvents on to the base granule to form a multilayered base granule.

8. The method of making the media or the feed composition for culturing cells of any of claims 1 or 3 to 4, wherein the second sprayer sprays a plurality of solvents on to the base particle to form a multilayered base particle.

9. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein the second sprayer sprays the plurality of solvents sequentially, with intermittent drying steps between each spraying step.

10. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein the second sprayer sprays the plurality of solvents sequentially, without any intermittent drying steps between each spraying step.

11. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein each solvent in the plurality of solvents has one component in each solvent.

12. The method of making the media or the feed composition for culturing cells of claim 11, wherein each solvent in the plurality of solvents has the same components.

13. The method of making the media or the feed composition for culturing cells of claim 11, wherein each solvent in the plurality of solvents has different components.

14. The method of any of the preceding claims, wherein said reactive species is selected from the group consisting of one or more trace elements, one or more reactive amino acids, one or more reactive amino acids, one or more metal salts, one or more acid soluble reactive groups, one or more alcohol soluble reactive groups and one or more pH modifier groups.

15. The method of any of the preceding claims, wherein said sensitive species is selected from the group consisting of one or more polyamines, one or more vitamins, one or more growth factor and one or more labile amino acids.

16. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein an inlet gas used in the method is at about temperature 20° C to 30° C.

17. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein an inlet gas used in the method is at about temperature 25° C.

18. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein the vitamins are selected from the group consisting of: vitamin B12, biotin, choline, folic acid, niacinamide, pyridoxine, riboflavin, thiamine, ascorbic acid and para-aminobenzoic acid (PABA).

19. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein the drying step is at about temperature 50° C to 60° C.

20. The method of making the media or the feed composition for culturing cells of any of the preceding claims, wherein the base particle or the base granule is dried to a moisture content of about 0.5% to 10%.

21. The method of making the media or the feed composition for culturing cells of any of the preceding claims of any preceding claim, wherein the solvent comprises a reactive species.

22. The method of making the media or the feed composition for culturing cells of any of the preceding claims of any preceding claim, wherein the solvent additionally comprises at least one antioxidant.

23. A layered base particle or a layered base granule comprising in its core a mixture of sensitive components, anti-oxidant components, and neutral components, wherein said sensitive components, anti-oxidant components, and neutral components are layered one by one on top of each other, and wherein said sensitive components or said neutral components or said anti-oxidant components form the central core of the layered base granule, wherein the sensitive components are components that may be destroyed by unwanted reaction with reactive species.

24. The method according to any of the claims 1 to 22, wherein at least one layer on the layered base particle or layered base granule comprises a reactive species and/or at least one layer on the base particle or base granule comprises a sensitive species.

25. The method of any one of claims 1 to 22 and 24, wherein said reactive species is selected from the group consisting of one or more trace elements, one or more reactive amino acids, one or more reactive amino acids, one or more metal salts, one or more acid soluble reactive groups, one or more alcohol soluble reactive groups and one or more pH modifier groups.

26. The method of claim 24, wherein said sensitive species is selected from the group consisting of one or more polyamines, one or more vitamins, one or more growth factor and one or more labile amino acids.

27. The method of any one claims 1 to 22 and 24 to 26, wherein the dry powder is selected from the group consisting of vitamins, bulk inorganic salts and sugars.

28. A method of culturing a cell in a liquid reconstituted from the layered base particle or layered base granule of claim 23, comprising:

i) reconstituting the layered base particle or layered base granule in a suitable liquid or buffer; wherein said layered base particle or layered base granule is a cell culture medium, feed, supplement or concentrate;

ii) culturing the cell is the reconstituted liquid under conditions favorable for the growth of the cell.

29. The method of culturing the cell of claim 28, wherein the culturing is used to produce increased amount of a polypeptide.

30. The method of culturing the cell of claims 28 to 29, wherein the polypeptide is a recombinant polypeptide.

31. The method of culturing the cell of claims 28 to 30, wherein the culturing increases product production, increasing cell growth, as compared to a culture with liquid media not made from the layered media particles.

32. A kit comprising:

i) a first container comprising a layered base particle or a layered base granule according to claim 23; wherein said layered base particle or said layered base granule is a cell culture medium, feed, supplement or concentrate;

ii) instructions for using the layered base particle or the layered base granule for cell culture.