

SUMMARY

[0005] One embodiment aspect described herein is a tableted composition comprising a cell culture medium, feed, or supplement comprising: amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and a lubricant, filler, binder, or combination thereof. In one aspect example, the tableted composition dissolves within about 10–30 minutes in water at 25 °C. In another aspect example, the composition comprises: 95–99 percent by mass of amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and 1–5 percent by mass of a lubricant comprising magnesium stearate. In another aspect example, the composition comprises: 90–99 percent by mass of amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and 1–5 percent by mass of a disintegrant comprising croscarmellose sodium; and 1–5 percent by mass of a lubricant comprising magnesium stearate.

[0006] Another embodiment aspect described herein is a composition comprising a tableted cell culture medium, feed, or supplement composition comprising: a media component comprising: 20–65 percent by mass carbohydrates; 20–40 percent by mass amino acids; 2–10 percent by mass inorganic salts or buffers; 1–5 percent by mass vitamins; 0.01–0.05 percent by mass trace minerals; and a tableting component comprising: 1–10 percent by mass of a lubricant, filler, binder, or combinations thereof. In one example aspect, the composition comprises: (a) 20–65 percent by mass of mono or disaccharides comprising glucose, fructose, lactose, trehalose, maltose, or sucrose; (b) 20–40 percent by mass of amino acids comprising alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, methionine, phenylalanine, proline, hydroxyproline, serine, threonine, tryptophan, valine, tyrosine, cysteine, lysine, salts thereof, or combinations thereof; (c) 2–10 percent by mass of salts of sodium, potassium, magnesium, calcium, ammonium, phosphate, carbonate, sulfate, or combinations thereof; (d) 1–5 percent by mass of vitamins comprising retinol (A), thiamine (B1), riboflavin (B2), niacinamide (B3), pantothenic acid (B5), pyridoxamine (B6), biotin (B7), folic acid (B9) cobalamin (B12), ascorbic acid (C), cholecalciferol (D), tocopherol (E), phyloquinone (K), choline, inositol, lipoic acid, para-aminobenzoic acid, salts thereof, or combinations thereof; (e) 0.01–0.05 percent by mass of trace elements including iron, manganese, copper, iodine, zinc, cobalt, fluoride, chromium, molybdenum, selenium, nickel, silicon, vanadium, salts thereof, or combinations thereof; (f) 1–5 percent by mass of magnesium stearate; and (g) 1–5 percent by mass of croscarmellose sodium.

[0007] In another [exampleaspect](#), the media component comprises an agglomerated dry powder. In another [exampleaspect](#), the tableted medium dissolves within about 10–30 minutes in water at 25°C. In another [exampleaspect](#), the tableted medium has a hardness of about 18–22 kp. In another [exampleaspect](#), the tableted medium has a mass of about 2.0 to 5.0 g. In another [aspectexample](#), the tableted medium upon reconstitution with water exhibits cell viability levels and expressed protein levels commensurate with an analogous non-tableted medium.

[0008] Another [embodimentaspect](#) described herein is a method for producing a tableted cell culture medium, feed, or supplement composition, the method comprising: (a) preparing a cell culture medium, feed, or supplement powder or agglomerated powder; (b) combining the media powder or agglomerated powder with one or more lubricants, fillers, binders, or combinations thereof; and (c) producing cell culture medium, feed, or supplement tablets using a tableting apparatus. In one [aspectexample](#), the cell culture medium, feed, or supplement is an agglomerated powder produced by fluid bed agglomeration. In another [aspectexample](#), the cell culture medium, feed, or supplement powder or agglomerated powder is combined with a lubricant. In another [aspectexample](#), the tableted composition comprises 95–99 percent by mass cell culture medium, feed, or supplement powder or agglomerated powder and 1–5 percent of one or more lubricants. In another [aspectexample](#), the lubricant comprises magnesium stearate. In another [aspectexample](#), the cell culture medium, feed, or supplement powder or agglomerated powder is combined with a lubricant and a disintegrant. In another [aspectexample](#), the tableted composition comprises 95–99 percent by mass cell culture medium, feed, or supplement powder or agglomerated powder; 1–5 percent of one or more lubricants; and 1–5 percent of one or more disintegrants. In another [aspectexample](#), the lubricant comprises magnesium stearate and the disintegrant comprises croscarmellose sodium. In another [aspectexample](#), the tablet has a mass of 2.0 to 5.0 g. In another [aspectexample](#), the tablet has a hardness of 18–22 kp. In another [aspectexample](#), the tablet dissolves within 10–30 min in water at 25 °C.

[0009] Another [embodimentaspect](#) described herein is a tableted cell culture medium, feed, or supplement produced by any of the methods described herein. In one [aspectexample](#), the tablet comprises: a media component comprising: 20–65 percent by mass carbohydrates; 20–40 percent by mass amino acids; 2–10 percent by mass inorganic salts or buffers; 1–5 percent by mass vitamins; 0.01–0.05 percent by mass trace minerals; and a tableting component comprising: 1–10 percent by mass of a lubricant, filler, binder, or combinations thereof. In another [aspectexample](#), the tablet comprises 95–99 percent by mass cell culture medium, feed, or supplement; and 1–5 percent of one or more lubricants. In another [aspectexample](#), the tablet comprises 90–99 percent by mass cell culture medium, feed, or supplement; 1–5 percent by mass

of a disintegrant comprising croscarmellose sodium; and 1–5 percent by mass of a lubricant comprising magnesium stearate. In another [aspectexample](#), the tablet has a mass of 2.0 to 5.0 g. In another [aspectexample](#), the tablet has a hardness of 18–22 kp. In another [aspectexample](#), the tablet dissolves within 10–30 min in water at 25°C.

[0010] Another [embodimentaspect](#) described herein is a kit comprising a package comprising one or more tablets of cell culture medium, feed, supplement, or buffer; a diluent; a receptacle suitable for reconstituting the one or more one or more tablets of cell culture medium, feed, supplement, or buffer; and instructions for use.

[0011] Another [embodimentexample](#) described herein is a method for making a cell culture medium, feed, supplement, or buffer from a tableted cell culture medium, feed, supplement, or buffer composition, the method comprising: (a) combining one or more tablets of cell culture medium, feed, supplement, or buffer with water until dissolved; (b) optionally, adding any supplements comprising amino acids, antibiotics, sera, or other cell culture media supplements; and (c) optionally, sterilizing the reconstituted cell culture medium, feeds, supplements, or buffers.

[Another aspect described herein is a method for making a cell culture medium, feed, supplement, or buffer from a tableted cell culture medium, feed, supplement, or buffer composition, the method comprising: \(a\) combining one or more tablets of cell culture medium, feed, supplement, or buffer with water until dissolved; and \(b\) optionally, adding any supplements comprising amino acids, antibiotics, sera, or other cell culture media supplements wherein the cell culture medium, feeds, supplements, or buffers are sterilized when needed.](#) In one [aspectexample](#), the sterilization comprises filtration or gamma irradiation. In another [aspectexample](#), the tablet dissolves within about 10–30 min in water at 25 °C.

[0012] Another [embodimentaspect](#) described herein is a cell culture medium, feed, supplement, or buffer prepared by a method described herein.

Another [embodimentexample](#) described herein is a system comprising a cell and a cell culture medium, feed, supplement, or buffer described herein.

[0013] Another [embodimentaspect](#) described herein is a method of culturing a cell in a liquid reconstituted from a tableted cell culture medium comprising: reconstituting a tableted cell culture medium, feed, or supplement in a suitable liquid or buffer; and culturing the cell in the reconstituted medium under conditions favorable for growth.

[0014] Another [aspectembodiment](#) described herein is a method of optimizing the concentration of a cell culture media component, the method comprising: measuring the concentration of one or more media components in a cell culture; determining whether the one or more media components are within an acceptable concentration range; if needed, supplementing the one or

more media components in the cell culture with a tableted cell culture media composition. In one [aspectexample](#), the measuring comprises a method selected from HPLC, mass spectrometry, ELISA, or standard curve assay. In another [aspectexample](#), the supplementation comprises adding the tableted media composition direct to the culture or dissolving the tableted media composition in a solvent and then adding the dissolved tableted media composition to the cell culture.

[0015] Another [embodimentexample](#) described herein is the use of a tableted cell culture medium, feed, or supplement for preparing a cell culture medium, feed, or supplement.

[0016] Another [embodimentexample](#) described herein is the use of a tableted cell culture medium, feed, or supplement for culturing cells. In another [aspectexample](#), the tableted cell culture medium, feed, or supplement for culturing is reconstituted and the cell cultured under favorable growth conditions. [Another aspect described herein is a composition described herein, wherein the media component further comprises a pH-opposing form of buffer salts.](#)

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1A shows exemplary media tablets formed from CHO CD EFFICIENTFEED B AGT Nutrient Supplement (GIBCO) and varying amounts of magnesium stearate. The tablets contain about 2.5 g of media, are 16 mm × 9.9 mm, and have a hardness of ~19 kp. See Table 4.

[0018] FIG. 1B shows exemplary media tablets formed from CHO CD EFFICIENTFEED B AGT Nutrient Supplement (GIBCO) and 2 percent magnesium stearate and their disintegration in water at 25°C. The disintegration was conducted with 50 g (20 tablets) in 926 mL of water, which is the recommended media preparation procedure. Tablets containing 2 percent by mass magnesium stearate disintegrated within 28 min and tablets containing 5 percent by mass magnesium stearate disintegrated within 38 min. See Table 5.

[0019] FIG. 2A shows CHO DG44 LH cells grown in CD OPTICHO (GIBCO) in shake flasks and supplemented with glucose (negative control), CHO CD EFFICIENTFEED B AGT (GIBCO) (positive control), or CHO CD EFFICIENTFEED B AGT Tablets (“Tablet Feeds”) containing 2 percent or 5 percent by mass magnesium stearate. Cell cultures supplemented with Tablet Feeds showed viable cell counts (e.g., $\sim 14 \times 10^6$ cells/mL) comparable to cell cultures supplemented with CHO CD EFFICIENTFEED B AGT (i.e., non-tableted feed; positive control). The unsupplemented cell cultures containing only glucose showed lower viable cell counts $\sim 10 \times 10^6$ cells/mL (negative control) as compared to the cell cultures supplemented with CHO CD EFFICIENTFEED B AGT.

[0020] FIG. 2B shows the same data as FIG. 2A as a scatter plot.

[0021] FIG. 3A shows IgG titers from the cell cultures discussed in FIG. 2A–2B. Cell cultures supplemented with Tablet Feeds showed comparable IgG production ($\sim 230 \mu\text{g/mL}$) to cell cultures supplemented with CHO CD EFFICIENTFEED B AGT (i.e., non-tableted feed; positive control). The unsupplemented cell cultures containing only glucose showed lower IgG production ($\sim 115 \mu\text{g/mL}$) as compared to cell cultures supplemented with CHO CD EFFICIENTFEED B AGT.

[0022] FIG. 3B shows the same data as FIG. 3A in a scatter plot.

[0023] FIG. 4 shows a flow chart for the large-scale manufacturing process for the production of media tablets.

CLAIMS

What is claimed:

1. A tableted composition comprising a cell culture medium, feed, or supplement comprising:
amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and
a lubricant, filler, binder, or combination thereof.
- ~~2. The composition of claim 1, wherein the tableted composition dissolves within about 10–30 minutes in water at 25°C.~~
- ~~3.2.~~ The composition of claim 1, wherein the composition comprises:
95–99 percent by mass of amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and
1–5 percent by mass of a lubricant comprising magnesium stearate or.
- ~~4.~~ ~~The composition of claim 1, wherein the composition comprises:~~
90–99 percent by mass of amino acids, salts, buffers, trace minerals, vitamins, carbohydrates, lipids, nucleic acids, proteins; and
1–5 percent by mass of a disintegrant comprising croscarmellose sodium; and
1–5 percent by mass of a lubricant comprising magnesium stearate.
- ~~5.3.~~ A composition comprising a tableted cell culture medium, feed, or supplement composition comprising:
a media component comprising:
20–65 percent by mass carbohydrates;
20–40 percent by mass amino acids;
2–10 percent by mass inorganic salts or buffers;
1–5 percent by mass vitamins;
0.01–0.05 percent by mass trace minerals; and
a tableting component comprising:
1–10 percent by mass of a lubricant, filler, binder, or combinations thereof.
- ~~6.4.~~ The composition of claim ~~35~~, wherein the composition comprises:
(a) 20–65 percent by mass of mono or disaccharides comprising glucose, fructose, lactose, trehalose, maltose, or sucrose;

- (b) 20–40 percent by mass of amino acids comprising alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, methionine, phenylalanine, proline, hydroxyproline, serine, threonine, tryptophan, valine, tyrosine, cysteine, lysine, salts thereof, or combinations thereof;
- (c) 2–10 percent by mass of salts of sodium, potassium, magnesium, calcium, ammonium, phosphate, carbonate, sulfate, or combinations thereof;
- (d) 1–5 percent by mass of vitamins comprising retinol (A), thiamine (B1), riboflavin (B2), niacinamide (B3), pantothenic acid (B5), pyridoxamine (B6), biotin (B7), folic acid (B9) cobalamin (B12), ascorbic acid (C), cholecalciferol (D), tocopherol (E), phyloquinone (K), choline, inositol, lipoic acid, para-aminobenzoic acid, salts thereof, or combinations thereof;
- (e) 0.01–0.05 percent by mass of trace elements including iron, manganese, copper, iodine, zinc, cobalt, fluoride, chromium, molybdenum, selenium, nickel, silicon, vanadium, salts thereof, or combinations thereof;
- (f) 1–5 percent by mass of magnesium stearate; and
- (g) 1–5 percent by mass of croscarmellose sodium.

~~7. The composition of claim 5, or~~ wherein the media component comprises an agglomerated dry powder.

~~8. The composition of any one of claims 5–7, wherein the tableted medium dissolves within about 10–30 minutes in water at 25°C.~~

~~9.5. The composition of any one of claims 5–83, wherein the tableted medium has a hardness of about 18–22 kp and/or:~~

~~10. The composition of any one of claims 5–9, wherein the tableted medium has a mass of about 2.0 to 5.0 g.~~

~~11. The composition of any one of claims 5–10, wherein the tableted medium upon reconstitution with water exhibits cell viability levels and expressed protein levels commensurate with an analogous non-tableted medium.~~

~~12.6. A method for producing a tableted cell culture medium, feed, or supplement composition, the method comprising:~~

- (a) preparing a cell culture medium, feed, or supplement powder or agglomerated powder;
- (b) combining the media powder or agglomerated powder with one or more lubricants, fillers, binders, or combinations thereof; and
- (c) producing cell culture medium, feed, or supplement tablets using a tableting apparatus.

~~13.7.~~ The method of claim ~~126~~, wherein the cell culture medium, feed, or supplement is an agglomerated powder produced by fluid bed agglomeration, and/or.

~~14.~~ ~~The method of claim 12 or 13,~~ wherein the cell culture medium, feed, or supplement powder or agglomerated powder is combined with a lubricant.

~~15.8.~~ The method of ~~any one of claims 12–145~~, wherein the tableted composition comprises 95–99 percent by mass cell culture medium, feed, or supplement powder or agglomerated powder and 1–5 percent of one or more lubricants, optionally.

~~16.~~ ~~The method of any one of claims 12–15,~~ wherein the lubricant comprises magnesium stearate.

~~17.9.~~ The method of claim ~~12–145~~, wherein the cell culture medium, feed, or supplement powder or agglomerated powder is combined with a lubricant and a disintegrant.

~~18.10.~~ The method of any one of claims ~~12–145~~ or ~~177~~, wherein the tableted composition comprises 95–99 percent by mass cell culture medium, feed, or supplement powder or agglomerated powder; 1–5 percent of one or more lubricants; and 1–5 percent of one or more disintegrants.

~~19.~~ ~~The method of any one of claims 12–14 or 17–18,~~ wherein the lubricant comprises magnesium stearate and the disintegrant comprises croscarmellose sodium.

~~20.~~ ~~The method of any one of claims 12–19, wherein the tablet has a mass of 2.0 to 5.0 g.~~

~~21.~~ ~~The method of any one of claims 12–20, wherein the tablet has a hardness of 18–22 kp.~~

~~22. The method of any one of claims 12–21, wherein the tablet dissolves within 10–30 min in water at 25°C.~~

~~23.11.~~ A tableted cell culture medium, feed, or supplement produced by the method of any one of claims ~~125–228~~.

~~24.12.~~ The tableted cell culture medium, feed, or supplement of claim 23, wherein the tablet comprises:

a media component comprising:

20–65 percent by mass carbohydrates;

20–40 percent by mass amino acids;

2–10 percent by mass inorganic salts or buffers;

1–5 percent by mass vitamins;

0.01–0.05 percent by mass trace minerals; and

a tableting component comprising:

1–10 percent by mass of a lubricant, filler, binder, or combinations thereof.

~~25.13.~~ The tableted cell culture medium, feed, or supplement of claim ~~24.12~~, wherein the tablet comprises 95–99 percent by mass cell culture medium, feed, or supplement; and 1–5 percent of one or more lubricants.

~~26. The tableted cell culture medium, feed, or supplement of claim 24, or~~ wherein the tablet comprises 90–99 percent by mass cell culture medium, feed, or supplement; 1–5 percent by mass of a disintegrant comprising croscarmellose sodium; and 1–5 percent by mass of a lubricant comprising magnesium stearate.

~~27.14.~~ The tableted cell culture medium, feed, or supplement of ~~any one of claims 23–269~~, wherein the tablet has a mass of 2.0 to 5.0 g ~~and/or~~.

~~28. The tableted cell culture medium, feed, or supplement of any one of claims 23–27,~~ wherein the tablet has a hardness of 18–22 kp.

~~29. The tableted cell culture medium, feed, or supplement of any one of claims 23–28, wherein the tablet dissolves within 10–30 min in water at 25°C.~~

~~30-15.~~ A kit comprising a package comprising one or more tablets of cell culture medium, feed, supplement, or buffer; a diluent; a receptacle suitable for reconstituting the one or more one or more tablets of cell culture medium, feed, supplement, or buffer; and instructions for use.

~~31-16.~~ A method for making a cell culture medium, feed, supplement, or buffer from a tableted cell culture medium, feed, supplement, or buffer composition, the method comprising:

- (a) combining one or more tablets of cell culture medium, feed, supplement, or buffer with water until dissolved; and
- (b) optionally, adding any supplements comprising amino acids, antibiotics, sera, or other cell culture media supplements; and
- (c) ~~optionally, sterilizing the reconstituted cell culture medium, feeds, supplements, or buffers~~ wherein the cell culture medium, feeds, supplements, or buffers are sterilized when needed.

~~32. The method of claim 31, wherein the sterilization comprises filtration or gamma irradiation.~~

~~33. The method of claim 31 or 32, wherein the tablet dissolves within about 10–30 min in water at 25°C.~~

~~34-17.~~ A cell culture medium, feed, supplement, or buffer prepared by the method of ~~any one of claims 31–33~~ 12.

~~35. A system comprising a cell and a cell culture medium, feed, supplement, or buffer of claim 34.~~

~~36-18.~~ A method of culturing a cell in a liquid reconstituted from a tableted cell culture medium comprising:
reconstituting a tableted cell culture medium, feed, or supplement in a suitable liquid or buffer; and
culturing the cell in the reconstituted medium under conditions favorable for growth.

~~37-19.~~ A method of optimizing the concentration of a cell culture media component, the method comprising:
measuring the concentration of one or more media components in a cell culture;

determining whether the one or more media components are within an acceptable concentration range;

if needed, supplementing the one or more media components in the cell culture with a tableted cell culture media composition.

38. ~~The method of claim 37, optionally~~ wherein the measuring comprises a method selected from HPLC, mass spectrometry, ELISA, or standard curve assay.

39. ~~The method of claim 37, or~~ wherein the supplementation comprises adding the tableted media composition direct to the culture or dissolving the tableted media composition in a solvent and then adding the dissolved tableted media composition to the cell culture.

~~40. Use of a tableted cell culture medium, feed, or supplement for preparing a cell culture medium, feed, or supplement.~~

~~41. Use of a tableted cell culture medium, feed, or supplement for culturing cells.~~

~~42. The use of claim 41, wherein the tableted cell culture medium, feed, or supplement for culturing is reconstituted and the cell cultured under favorable growth conditions.~~

20. A composition of claims 3-4, wherein the media component further comprises a pH-opposing form of buffer salts.