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(54) Title: A PROCESS TO PRODUCE A PHARMACEUTICAL COMPOSITION

(57) Abstract: The present invention relates to a mammalian cell culture process to modulate a pharmaceutical composition of a monoclonal antibody composition comprising galactosylated glycoform of the antibody, the process comprising 5 culturing the mammalian cells within a pH range of about 6.7 to about 7.4, performing a temperature shift from a first culture temperature to a second culture temperature, supplementing the cell culture with manganese or galactose, thereby obtaining an antibody composition comprising increased percentage of galactosylated glycoforms. Further, the cell culture process 10 disclosed in the present invention comprises culturing mammalian cells within a pH range of about 6.7 to about 7.4, performing a temperature shift from a first culture temperature to a second culture temperature, supplementing the cell culture with manganese or galactose, thereby obtaining a biosimilar monoclonal antibody composition comprising galactosylated glycoforms of the 15 biosimilar monoclonal antibody at a target/predetermined range as of that of the reference product.

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A PROCESS TO PRODUCE A PHARMACEUTICAL COMPOSITION

FIELD OF INVENTION

The Biological material used in the invention was not obtained from India.

The present invention relates to a cell culture process for culturing mammalian cells producing a pharmaceutical composition. The invention provides a mammalian cell culture process to modulate a pharmaceutical composition of a monoclonal antibody comprising culturing the mammalian cells, supplementing the cell culture with manganese or galactose. In particular, the invention provides a cell culture process to obtain a monoclonal antibody composition comprising galactosylated glycoform at a target/predetermined range.

BACKGROUND OF THE INVENTION

In cancer therapy, immune checkpoints have attracted much attention as targets of immunotherapy. In 2014, US Food and Drug Administration (US FDA) approved two monoclonal antibodies (mAbs) targeting the immune checkpoint PD-1; nivolumab and pembrolizumab. (*Lee, J., et al. Structural basis of checkpoint blockade by monoclonal antibodies in cancer immunotherapy. Nat Commun 7, 13354, 2016; Tan, S., et al. An unexpected N-terminal loop in PD-1 dominates binding by nivolumab. Nat Commun 8, 14369, 2017*). Nivolumab, a human IgG4 monoclonal antibody binds to PD-1 and is approved for treatment of melanoma; non-small cell lung cancer (NSCLC); malignant pleural mesothelioma (MPM); renal cell carcinoma (RCC); and classical Hodgkin lymphoma (cHL). It is produced in mammalian cells, Chinese hamster ovary (CHO) cells, in which the post-translational modifications (PTMs) is an integral part of the mabs produced. Among the PTMs, glycosylation plays a key role in the effector functions of the antibody including its biological activity, efficacy, stability, immunogenicity, clearance rate, antibody-dependent cellular cytoxicity (ADCC), and complement-dependent cytoxicity (CDC). (*Torrente-López, A.; et al. Comprehensive*

Analysis of Nivolumab, A Therapeutic Anti-PD-1 Monoclonal Antibody: Impact of Handling and Stress. Pharmaceutics 14, 692, 2022).

The two major types of glycosylation in mammalian expression systems are N-linked glycosylation, in which glycans are attached to the asparagine of the recognition sequence Asn-X-Thr/Ser, where "X" is any amino acid except proline, and O-linked glycosylation in which glycans are attached to serine or threonine. The N-linked glycosylation results in heterogeneity in antibody glycoforms which affect the efficacy and safety of the antibody. Hence, various studies have been done to understand and characterize the glycoform distributions in antibodies during their production (*Radhakrishnan, D., A.S. Robinson, and B.A. Ogunnaike, Controlling the Glycosylation Profile in mAbs Using Time-Dependent Media Supplementation. Antibodies, 2017. 7(1): p. 1*)

'Biosimilars', sometimes called 'similar biological medicinal product' or 'follow-on biologic' or 'subsequent entry biologic', include therapeutic mAbs which are similar to the already approved/licensed therapeutic product (the 'reference product'). Regulatory agencies mandate that biosimilars must demonstrate high similarity to the reference product, in terms of quality characteristics, biological activity, safety and efficacy, in order to have marketing approval *(Sullivan, P.M. and L.M. DiGrazia, Analytic characterization of biosimilars. Am J Health Syst Pharm, 2017. 74(8): p. 568-579; Guttman et. al. Assessing Glycosimilarity of Biotherapeutics. 2018 https://sciex.com/content/dam/SCIEX/pdf/tech-notes/all/Glycosimilarity.pdf)*.

Given the importance of glycosylation in the regulatory approval of reference products and biosimilars alike, much efforts have been undertaken to understand the cell culture process parameters which may have any effect on the glycosylation pattern of the therapeutic products. Previous studies have demonstrated that glycosylation of mAbs can be influenced by various factors such as pH, temperature, dissolved oxygen, ammonia, and media supplements such as sugar and manganese chloride. These studies focused on individual factors, establishing empirical relationships between the

individual factor in question and the specific set of glycoform species it affects *(Radhakrishnan, D., A.S. Robinson, and B.A. Ogunnaike, Controlling the Glycosylation Profile in mAbs Using Time-Dependent Media Supplementation. Antibodies, 2017. 7(1): p. 1).*

Therefore, the present invention relates to a cell culture process for producing an antibody composition, the process comprising culturing mammalian cells at a pH range of 6.7 to 7.4, performing a temperature shift from a first culture temperature to a second culture temperature, supplementing manganese or galactose in the cell culture, thereby obtaining an antibody composition comprising galactosylated glycoform, wherein the percentage of galactosylated glycoform increases with the supplementation of the said supplements.

SUMMARY OF THE INVENTION

The present invention relates to a cell culture process for producing a pharmaceutical monoclonal antibody composition, the process comprising culturing mammalian cells expressing the monoclonal antibody within a pH range of about 6.7 to about 7.4, performing a temperature shift from a first culture temperature to a second culture temperature, supplementing manganese or galactose in the cell culture, thereby obtaining an antibody composition comprising increased percentage of galactosylated glycoforms. Further, the present invention discloses that the obtained antibody composition comprises galactosylated glycoform wherein the percentage of galactosylated glycoforms is at a target/predetermined range.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term “about” refers to a range of values that are similar to the stated reference value to a range of values that fall within 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 percent or less of the stated reference value.

The term “antibody” or “monoclonal antibody” refers to an intact antibody or an antigen binding fragment thereof.

The term “antibody composition” refers to a population of antibody molecules or fragments thereof that is produced by mammalian cell culture. The population of antibody molecules may have one or several post translational modifications (PTM), imparting the antibody molecules a different molecular weight, charge, solubility or combinations thereof.

The term "biosimilar" refers to a recombinant pharmaceutical protein, commonly with identical amino acid sequence to a reference product that contains, similar, very similar to or same post-translational modifications as the reference product yielding no clinically meaningful difference in terms of safety, purity and potency.

The term “cell culture process” as used herein refers to a process of culturing a population of cells that are capable of producing recombinant protein of interest or antibody.

The term “galactosylated glycoform” or “Gal’ refer to antibodies containing terminal galactose residues such as G1A, G1B, G1AF, G1BF, G2, G2F and G2SF.

The term “glycoform” or “glycovariant” used interchangeably herein refers to different molecular variants of an antibody resulting due to variable glycan structure attached and/or glycan attachment site occupancy on the antibody.

The term “glycan” refers to monosaccharide or polysaccharide moiety attached to another molecule.

The term “pH shift” refers to the change in pH range during the cell culture process, which includes modification in either or both of the upper and lower limits of the pH range.

The term "reference product" refers to a currently or previously marketed recombinant protein, also described as the "originator product" or "branded product" serving as a comparator in the studies.

The term "supplementing" or “supplementation” as used herein refers to any addition made to cell culture medium/feed to achieve the goals described in this disclosure.

The term “target/predetermined levels” refers to the glycosylation levels of the ‘reference product’.

The term “temperature shift” refers to the change in temperature during the cell culture process.

DETAILED DESCRIPTION OF THE EMBODIMENTS

The present invention provides a cell culture process for culturing mammalian cells expressing an antibody, the process comprising culturing the cells at a pH range of 6.7 to 7.4 by lowering of temperature of the cell culture from a first temperature to a second temperature, and supplementing manganese or galactose to the cell culture to obtain antibody composition comprising galactosylated variants.

Any mammalian cell or cell type which is suitable for expression of recombinant proteins in a cell culture medium may be used for the present invention. Non-limiting examples of mammalian cells that may be used with the present invention include Chinese hamster ovary (CHO) cells, baby hamster kidney (BHK21) cells and murine myeloma cells (NS0 and Sp2/0) human retinoblasts (PER.C6 cell line), human embryonic kidney cell line (HEK-293 cell line) *(Dumont, J., et al., Human cell lines for biopharmaceutical manufacturing: history, status, and future perspectives. Crit Rev Biotechnol, 2016. 36(6): p. 1110-1122)*. In a preferred embodiment, CHO cell lines expressing recombinant proteins may be used in accordance with the present invention.

Certain glycosylation profile of the pharmaceutical monoclonal antibody (mAb) are desirable based on its mechanism of action as the glycosylation profile effects the stability, safety and efficacy of the antibody. In an embodiment, the cell culture process of the present invention may be used to produce an antibody composition comprising galactosylated glycoform at a target/predetermined range.

Cell culture medium is understood by those skilled in the art to refer to a nutrient solution in which cells, such as animal or mammalian cells, are grown. A cell culture medium generally includes one or more of the following components: an energy source (e.g., a carbohydrate such as glucose); amino acids; vitamins; lipids or free fatty acids; and trace elements, e.g., inorganic compounds or naturally occurring elements in the micromolar range. Cell culture medium can also contain additional components, such as hormones and other growth factors (e.g., insulin, transferrin, epidermal growth factor, serum, and the like); salts (e.g., calcium, magnesium and phosphate); sugars (e.g. mannose, galactose, fucose); amino acids (glutamine); buffers (e.g., HEPES); nucleosides and bases (e.g., adenosine, thymidine, hypoxanthine); antibiotics (e.g., gentamycin); and cell protective agents (e.g., a Pluronic polyol (Pluronic F68). Commercially available media can be utilized in accordance with the present invention, for example, Dulbecco's Modified Eagles Medium (DMEM, Sigma-Aldrich); RPMI-1640 Medium (Sigma-Aldrich); EX-CELL® Advanced CHO Fed-batch Medium (Sigma-Aldrich); Cell Boost™ 7a and 7b (GE Healthcare Bio-Sciences AB). One skilled in the art would appreciate that some cell culture media are suited to support cells through their initial growth phase (basal medium) while some sustain cells through the later growth phase and production phase of cell culture (feed medium), and would be able to choose appropriate culture medium.

The methods described in the present invention are in recognition of the fact that various parameters of the cell culture process may be used to obtain antibody composition of desired glycosylation profile. In an embodiment, the

cell culture process envisages culturing the cells within a pH range of about 6.7 to about 7.4, performing a temperature shift and supplementing manganese or galactose.

A person of ordinary skill in the art would be able to characterize and analyse the various antibody variants present in the antibody composition produced by the cell culture process described herein using the state of the art techniques.

In an embodiment, the present invention discloses a cell culture process for producing an antibody composition, wherein the said process comprises

a) providing mammalian cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with manganese or galactose

e) recovering the said recombinant antibody composition

wherein the antibody composition obtained comprises of increased percentage of galactosylated glycoforms as compared to the antibody composition obtained from a cell culture process devoid of step (d).

In an embodiment, the present invention discloses a cell culture process for producing an antibody composition, wherein the said process comprises

a) providing mammalian cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with manganese or galactose

e) recovering the said recombinant antibody composition

wherein the antibody composition obtained comprises of increased percentage of galactosylated glycoforms,

wherein the increased percentage of galactosylated glycoforms in the antibody composition obtained using the present invention is about 30% to about 42%, as compared to the antibody composition obtained from a cell culture process devoid of step (d).

In any of the embodiments mentioned above, the claimed process comprises supplementing the cell culture with about 0.0625 uM to about 2 uM manganese; or about 1 g/L to about 10 g/L galactose.

In an embodiment, the present invention discloses a cell culture process for producing a biosimilar monoclonal antibody composition, wherein the said process comprises

a) providing mammalian cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with manganese or galactose

e) recovering the said recombinant antibody composition

wherein the biosimilar monoclonal antibody composition obtained comprises of galactosylated glycoforms at a target/predetermined range.

In an embodiment, the target/predetermined percentage of galactosylated glycoforms for the biosimilar monoclonal antibody composition is about 31%.

In an embodiment, the present invention discloses a cell culture process for producing a biosimilar monoclonal antibody composition, wherein the said process comprises

a) providing mammalian cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with about 0.0625 uM to about 0.125 uM manganese; or about 2 g/L to 4 g/L galactose

e) recovering the said recombinant antibody composition

wherein the biosimilar monoclonal antibody composition obtained comprises of galactosylated glycoforms at about 31%.

In an embodiment, the present embodiment discloses a cell culture process for producing a biosimilar monoclonal antibody composition, wherein the said process comprises

a) providing mammalian cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with about 2.5 g/L galactose

e) recovering the said recombinant antibody composition

wherein the biosimilar monoclonal antibody composition obtained comprises of galactosylated glycoforms at about 31%.

In any of the embodiments mentioned above, the difference between the first culture temperature and the second culture temperature of the cell culture is about 4.5°C. In another embodiment, the culture temperature before the temperature shift is about 36.5°C and the culture temperature after the temperature shift is about 32°C.

In the embodiments mentioned above, the temperature shift is performed at day 5 of the cell culture.

In the embodiments mentioned above, the supplementation of manganese or galactose is performed on the same or different day as that of the temperature shift of the cell culture.

In the embodiments mentioned above, the supplementation of manganese or galactose is performed on day 5 or day 7 or day 9 of the cell culture.

In any embodiments mentioned above, the manganese is supplemented as manganese chloride.

In yet another embodiment, the antibody produced using the present invention is an anti PD-1 antibody. In a preferred embodiment, the antibody produced using the present invention is nivolumab.

Those skilled in the art will recognize that several embodiments are possible within the scope and spirit of this invention. The invention will now be described in greater detail by reference to the following non-limiting examples. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

Example I:

An anti-PD 1 antibody having a heavy chain and light chain as described in US8008449B2, with the sequence set forth in SEQ ID NO: 4 and SEQ ID NO: 11 respectively, was cloned and expressed in a recombinant CHO (rCHO) cell line using techniques described in detail in "Molecular Cloning: A Laboratory Manual (Fourth Edition)". rCHO cells expressing the antibody were seeded at a density of about 0.9 million cells/mL in basal cell culture medium and cultured at an initial temperature of 36.5°C. The pH range of the cell culture is maintained between pH 6.9 to 7.2. On day 5, a temperature shift was performed, thereby reducing the culture temperature to 32°C and the pH range was maintained at 6.7 to 7.4. Feed medium was added on day 3, 5, 7, 9 and 11. The culture was harvested on day 12.

Example II:

The cell culture process described in Example I was carried with following modifications. On day 7, the cell culture was supplemented with about 0.0625 µM to 2 µM manganese chloride.

Example III:

The cell culture process described in Example I was carried with following modifications. On day 7, the cell culture was supplemented with about 2 g/L to 10 g/L galactose.

Example IV:

The cell culture process described in Example I was carried with following modifications. The cell culture process described in Example I was carried with following modifications. On day 9, the cell culture was supplemented with about 1 g/L to 4 g/L galactose.

Example V:

The cell culture process described in Example I was carried with following modifications. On day 7, the cell culture was supplemented with about 2.5 g/L galactose.

The antibody composition comprising % of galactosylated glycoforms obtained in the examples I to IV and V is depicted in Table 1 and 2 respectively.

The percentage of galactosylated glycoforms in the reference product (RMP) is about 31 %.

Table 1. The composition of galactosylated glycoforms of the anti PD-1 antibody obtained with supplementation of manganese or galactose in different days.

Example	Day of supplementation	Galactose Conc. (g/L)	$MnCl_2$ Conc. (µM)	Galactosylated glycan (%)
I	-	-	-	22.6
II	7	-	0.0625	29.9
II	7	-	0.125	33.6
II	7	-	0.25	37.7
II	7	-	0.5	42.0
II	7	-	1	42.1
II	7	-	2	42.6
III	7	2	-	29.5
III	7	4	-	31.4
III	7	6	-	33.1
III	7	8	-	33.3
III	7	10	-	34.3
IV	9	1	-	34.0
IV	9	2	-	35.0
IV	9	4	-	37.2

Table 2. The composition of galactosylated glycoforms of the anti PD-1 antibody with supplementation of 2.5 g/L galactose on day 7.

Example	Day of supplementation	Galactose Conc. (g/L)	$MnCl_2$ Conc. (µM)	Galactosylated glycan (%)
VI	7	2.5	-	31.8
VI	7	2.5	-	30.9
VI	7	2.5	-	31.0
VI	7	2.5	-	31.6
VI	7	2.5	-	30.6
VI	7	2.5	-	32.0
VI	7	2.5	-	33.1
VI	7	2.5	-	29.5
VI	7	2.5	-	30.2
			Average	31.2

What is claimed is:

1. A cell culture process for producing an antibody composition, wherein the said process comprises

a) providing recombinant CHO cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with manganese or galactose

e) recovering the said recombinant antibody composition

wherein the antibody composition obtained comprises of increased percentage of galactosylated glycoforms as compared to the antibody composition obtained from a cell culture process devoid of step (d).

2. The cell culture process as claimed in claim 1, wherein the cell culture is supplemented with about 0.0625 uM to about 2 uM manganese; or about 1 g/L to about 10 g/L galactose.

3. The increased percentage of galactosylated glycoforms as claimed in claim 1 is about 30% to about 42%.

4. The temperature shift as claimed in claim 1, wherein the culture temperature before the temperature shift is about 36°C and the culture temperature after the temperature shift is about 32°C.

5. A cell culture process for producing a biosimilar monoclonal antibody composition, wherein the said process comprises

a) providing recombinant CHO cells expressing the said antibody

b) performing a temperature shift during the cell culture from a first culture temperature to a second culture temperature, wherein the second culture temperature is lower than the first culture temperature

c) performing pH shift from a pH range of about 6.7 to about 7.2 to a pH range of about 6.7 to about 7.4

d) supplementing the cell culture with about 0.0625 uM to about 2 uM manganese; or about 1 g/L to about 10 g/L galactose

e) recovering the said recombinant antibody composition

wherein the biosimilar monoclonal antibody composition obtained comprises of galactosylated glycoforms at a target/predetermined range.

6. The temperature shift as claimed in claim 5, wherein the culture temperature before the temperature shift is about 36°C and the culture temperature after the temperature shift is about 32°C.

7. The supplementation of galactose as claimed in claim 5 is preferably about 2.5 g/L.

8. The target/predetermined percentage of galactosylated glycoforms for the biosimilar monoclonal antibody composition obtained with supplementation of galactose as claimed in claim 7 is about 31%.

9. The antibody as claimed in claim 1 is an anti-PD-1 antibody.

10. The biosimilar monoclonal antibody composition as claimed in claim 5 is an anti-PD-1 antibody.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2024/050297

A. CLASSIFICATION OF SUBJECT MATTER
C12P21/08,C07K16/00,C12N5/16 Version=2024.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12P, C07K, C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2023021532A1 (DR. REDDY'S LABORATORIES LIMITED) 23 FEBRUARY 2023 (23-02-2023) Whole Document especially examples 1 and 4 and table 1	1-8
Y	Whole Document	9, 10
Y	WO2017021493A1 (RICHTER GEDEON NYRT.) 09 FEBRUARY 2017 (09-02-2017) Whole document especially abstract, claims 1, 2, 10-13	9,10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT
Information on patent family members

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Citation	Pub.Date	Family	Pub.Date
WO 2023021532 A1	23-02-2023	IN 202141037886 A	24-02-2023
		EP 4388119 A1	26-06-2024
WO 2017021493 A1	09-02-2017	JP 6971221 B2	24-11-2021
		US 20180230228 A1	16-08-2018
		EP 3331911 A1	13-06-2018
		CA 2994611 A1	09-02-2017