to the invention can be immensely reduced by a factor of about 20 to about 50 in comparison to the prior art measurements using aqueous solutions of the respective plant or yeast hydrolysate samples. Therefore, e.g. a small amount of soy hydrolysate powder from a lot can be used as a sample to predict the performance of the whole lot.

Furthermore, these 2D-fluorescence spectroscopy results of a given plant or yeast hydrolysate sample, in particular derived from a plant or yeast hydrolysate lot, could be correlated with manufacturing data of a protein when produced in a cell culture medium comprising an amount of said plant or yeast hydrolysate lot.

A benefit of the invention is also the fact that there is no need to combine various spectral analysis methods as described in the prior art.

SUMMARY

In one example, there is disclosed a method of predicting a performance characteristic of a plant or yeast hydrolysate measured in powder form comprising the steps of a) providing a training set comprising a plurality of plant or yeast hydrolysate samples, each sample having a predetermined value of a manufacturing parameter of interest, b) irradiating a sample of said training set with light of a plurality of wavelengths in a predetermined range, c) determining at least one measured value indicative of radiation emitted from the sample, d) repeating steps b) and c) for all samples of said training set, e) performing multivariate data analysis of the at least one measured value determined for each of the plurality of samples and corresponding predetermined manufacturing parameters of interest to obtain model parameters correlating the at least one measured value determined for each of the plurality of samples with the corresponding predetermined manufacturing parameters of interest, f) obtaining information correlated to the manufacturing parameter of interest of a new sample different from the samples of said training set from an at least one measured value indicative of radiation emitted from the sample according to step c) after irradiating said sample according to step b) by using those model parameters obtained in step e), g) obtaining predictive information related to the performance characteristic of the new sample by determining whether said manufacturing parameter of interest falls into a predetermined range. The present disclosure describes a method of predicting a performance characteristic of a plant or yeast hydrolysate, wherein a plant or yeast hydrolysate sample is measured with 2D fluorescence spectroscopy in powder form. Preferably the plant or yeast hydrolysate sample, in particular a soy hydrolysate sample, is an amount of plant or yeast hydrolysate of a commercially purchased lot. Said method comprises the steps for

providing a model based on a predetermined value of a manufacturing parameter of interest.

For this purpose a training set consisting of predetermined manufacturing parameter of interest (e.g volumetric productivity parameter, virus titer or cell number) and fluorescence spectroscopic data is used. The fluorescence spectroscopic data is correlated to the values of the manufacturing parameter of interest to obtain a calibration model/model parameters by applying multivariate data analysis. This calibration model is being used to predict the manufacturing parameter of interest for new samples dedicated for the manufacturing process. This prediction is used for a decision to accept or reject the lot which corresponds to the respective sample for use in the manufacturing process or for further evaluation depending on the pre-defined range of the manufacturing parameter of interest.

In another example, there is disclosed a method for preparing a cell culture medium, comprising the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method according to claims 1 to 10 and bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium. In yet another aspect, the present invention refers to a method for cultivating cells, comprising the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method as disclosed herein, bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium, cc) providing one or more cells that produce a recombinant target protein, dd) culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell culture medium, to form a cell culture. In a further example, there is disclosed a method for producing a recombinant target protein, comprising the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method as disclosed herein, bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium, aa) providing one or more cells that produce a recombinant target protein, ee)culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell medium, such that a recombinant target protein is expressed and excreted from the cells into a culture supernatant, and recovering said target protein. In another example, there is disclosed a method for producing an immunogenic composition comprising a virus or virus antigen, wherein the method comprises the steps of aa) providing a plant or yeast

hydrolysate having a high performance characteristic as determined by a method as disclosed herein and bb)mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium, ff)providing a culture of cells, gg) infecting the cells with a virus; hh) incubating the infected cells to propagate the virus; jj) harvesting the virus or virus antigen produced; and kk) preparing an immunogenic composition from the harvested virus or virus antigen. In yet another example, there is disclosed use of the method as disclosed herein for preparation of a cell culture medium, preferably an animal protein free cell culture medium, comprising at least one of said plant or yeast hydrolysate having a high performance characteristic as determined by the method as disclosed herein. In one aspect, the present invention refers to a method of predicting a performance characteristic of a plant or yeast hydrolysate in a cell culture process when added to a culture medium as a nutrient, measured in powder form, comprising the steps of a) providing a training set comprising a plurality of plant or yeast hydrolysate samples, each sample having a corresponding predetermined value of a manufacturing parameter of interest, b) obtaining a 2D fluorescent spectrum of each plant or years hydrolysate sample, in powder form, in said training set by 1) irradiating a plant or yeast hydrolysate sample, in powder form, of said training set with light of a plurality of wavelengths in a predetermined range, 2) determining at least one measured value indicative of radiation emitted from the plant or yeast hydrolysate sample in response to said irradiating, and 3) repeating steps 1) and 2) for each plant or yeast hydrolysate sample of said training set, c) performing multivariate data analysis of only said 2D fluorescent spectra obtained for each plant or yeast hydrolysate sample in the plurality of plant or yeast hydrolysate samples and said corresponding predetermined manufacturing parameters of interest to obtain model parameters correlating the at least one measured value determined for each of the plurality of plant or yeast hydrolysate samples with the corresponding predetermined manufacturing parameters of interest, d) obtaining information correlated to the manufacturing parameter of interest of a new plant or yeast hydrolysate sample different from the plurality of plant or yeast hydrolysate samples of said training set by applying a 2D fluorescent spectrum of the new plant or yeast hydrolysate sample including at least one measured value indicative of radiation emitted from the new plant or yeast hydrolysate sample after irradiating said new plant or yeast hydrolysate sample to the model parameters obtained in step c), and e) obtaining predictive information related to the performance characteristic of the new plant or yeast hydrolysate sample by determining whether said information correlated to the manufacturing parameter of interest falls into a predetermined range. In another aspect, the present invention refers to a method for preparing a cell culture medium, comprising

the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method as disclose herein and bb)mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium. In yet another aspect, the present invention refers to a method for cultivating cells, comprising the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method as disclosed herein, bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium, cc) providing one or more cells that produce a recombinant target protein, dd) culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell culture medium, to form a cell culture. In a further aspect, the present invention refers to a method for producing a recombinant target protein, comprising the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method as disclosed herein, bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium, aa) providing one or more cells that produce a recombinant target protein, ee) culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell medium, such that a recombinant target protein is expressed and excreted from the cells into a culture supernatant, and recovering said target protein. In another aspect, the present invention refers to a method for producing an immunogenic composition comprising a virus or virus antigen, wherein the method comprises the steps of aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method disclosed herein, and bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium, ff) providing a culture of cells, gg) infecting the cells with a virus; hh) incubating the infected cells to propagate the virus; jj) harvesting the virus or virus antigen produced; and kk) preparing an immunogenic composition from the harvested virus or virus antigen. In a further aspect, the present invention refers to use of the method as disclosed herein for preparation of a cell culture medium, preferably an animal protein free cell culture medium, comprising at least one of said plant or yeast hydrolysate having a high performance characteristic as determined by the method as disclosed herein.

A further example is a method for preparation of a cell culture medium, preferably an animal protein free cell culture medium, a method for cultivating cells, a method for

producing a recombinant target protein, a method for producing an immunogenic composition, whereby the above method of predicting a

CLAIMS

1. A method of predicting a performance characteristic of a plant or yeast hydrolysate in a cell culture process when added to a culture medium as a nutrient, measured in powder form, comprising the steps of:

a) providing a training set comprising a plurality of plant or yeast hydrolysate samples, each sample having a corresponding predetermined value of a manufacturing parameter of interest,

b) obtaining a 2D fluorescent spectrum of each plant or years hydrolysate sample, in powder form, in said training set by:

1) irradiating a plant or yeast hydrolysate sample, in powder form, of said training set with light of a plurality of wavelengths in a predetermined range,

2) determining at least one measured value indicative of radiation emitted from the plant or yeast hydrolysate sample in response to said irradiating, and

3) repeating steps 1) and 2) for each plant or yeast hydrolysate sample of said training set,

c) performing multivariate data analysis of only said 2D fluorescent spectra obtained for each plant or yeast hydrolysate sample in the plurality of plant or yeast hydrolysate samples and said corresponding predetermined manufacturing parameters of interest to obtain model parameters correlating the at least one measured value determined for each of the plurality of plant or yeast hydrolysate samples with the corresponding predetermined manufacturing parameters of interest,

d) obtaining information correlated to the manufacturing parameter of interest of a new plant or yeast hydrolysate sample different from the plurality of plant or yeast hydrolysate samples of said training set by applying a 2D fluorescent spectrum of the new plant or yeast hydrolysate sample including at least one measured value indicative of radiation emitted from the new plant or yeast hydrolysate sample after irradiating said new plant or yeast hydrolysate sample to the model parameters obtained in step c), and

e) obtaining predictive information related to the performance characteristic of the new plant or yeast hydrolysate sample by determining whether said information correlated to the manufacturing parameter of interest falls into a predetermined range.

2. The method according to claim 1, wherein the predetermined range of wavelengths of light of irradiating a sample of said training set lies within a range of 290 to 550 nm.

3. The method according to claim 1 or 2, further comprising the step of performing data processing of the at least one measured value determined for each of the plurality of samples to obtain processed values, and using said processed values to perform multivariate data analysis in step c).

4. The method according to any of the preceding claims, wherein said predetermined range for obtaining predictive information related to the performance characteristic of said new sample by determining whether said manufacturing parameter of interest falls into it according to step e) comprises the following steps:

(i) setting an acceptable performance of a predetermined value of a manufacturing parameter of interest to be 100 %, and

(ii) determining whether said information correlated to the manufacturing parameter of interest obtained after step d) is greater than 100 % or not, wherein a performance of greater than 100% is a high performance and a performance of less than 100% is a low performance.

5. The method according to any of the preceding claims, wherein the plant hydrolysate is selected from the group consisting of soy hydrolysate and wheat hydrolysate.

6. The method according to any of the preceding claims, wherein the manufacturing parameter of interest is determined on the basis of a cell culture and is selected from the group consisting of the volumetric productivity parameter, the virus titer and the cell number.

7. The method according to any of the preceding claims, wherein step c) further comprises data pre-processing and multivariate data analysis that is performed according to a validated chemometric model.

8. The method according to claim 7, wherein the data pre-processing comprises at least one of the following steps:

(iii) wavelength selection and

(iv) scaling.

9. The method according to claim 7 or 8, wherein the validated chemometric model is calculated on the basis of the data as received from a pre-processing step further comprising the calculation of a chemometric model, the evaluation of said chemometric model, optionally the remodeling of the chemometric model by using specifically selected VIP-variables and the validation of the chemometric model with a new fluorescence data set obtainable from 2D-multiwavelength fluorescence analysis of a plant or yeast hydrolysate which performance is to be predicted.

10. A method for preparing a cell culture medium, comprising the steps of:

aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method according to claims 1 to 9 and

bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or

adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium.

11. A method for cultivating cells, comprising the steps of:

aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method according to claims 1 to 9,

bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or

adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form the cell culture medium,

cc) providing one or more cells that produce a recombinant target protein,

dd) culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell culture medium, to form a cell culture.

12. A method for producing a recombinant target protein, comprising the steps of:

aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method according to claims 1 to 9,

bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or
adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium,

aa) providing one or more cells that produce a recombinant target protein,

ee) culturing the one or more cells in the plant or yeast hydrolysate supplemented cell culture medium, preferably a basal cell medium, such that a recombinant target protein is expressed and excreted from the cells into a culture supernatant, and recovering said target protein.

13. A method for producing an immunogenic composition comprising a virus or virus antigen, wherein the method comprises the steps of:

aa) providing a plant or yeast hydrolysate having a high performance characteristic as determined by a method according to claims 1 to 9 and

bb) mixing the hydrolysate of step aa) with other cell culture medium components to form the cell culture medium or
adding the plant or yeast hydrolysate of step aa) to a basal cell culture medium to form a cell culture medium,

ff) providing a culture of cells,

gg) infecting the cells with a virus;

hh) incubating the infected cells to propagate the virus;

jj) harvesting the virus or virus antigen produced; and

kk) preparing an immunogenic composition from the harvested virus or virus antigen.

14. The method according to claims 11 to 13, wherein the cells are selected from the group consisting of mammalian cells, insect cells, avian cells, bacterial cells and yeast cells.

15. The method according to claim 12, wherein the cell/target protein combination is selected from the group consisting of CHO cells/coagulation factor VIII, factor VII, factor IX, factor II and factor X.

16. The method according to claim 13, wherein the cell/virus combination is selected from the group consisting of Vero cell/attenuated vaccinia, Vero cell/vaccinia, Vero cell/hepatitis A, Vero cell/influenza virus, Vero cell/West Nile virus, Vero cell/SARS virus, and chicken embryo cells/FSME virus, chicken embryo cells / MVA, chicken embryo cells / recombinant MVA, avian cells / FSME virus, avian cells / MVA and avian cells / recombinant MVA.

17. Use of the method according to claims 1 to 9 for preparation of a cell culture medium, preferably an animal protein free cell culture medium, comprising at least one of said plant or yeast hydrolysate having a high performance characteristic as determined by the method according to claims 1 to 9.