

a treatment composition having a predetermined property for inactivation of a virus, confirming that the treatment composition exhibits the predetermined property, transferring the treatment composition to a treatment vessel that includes a static mixer, incubating the treatment composition in the treatment vessel at a predetermined temperature while the treatment composition flows at a predetermined rate and contacts the static mixer, and collecting the treatment composition from the treatment vessel, wherein the steps are carried out continuously, as taught, for example, by Coffman et al., WO 2015/158776. Such methods may include a control burden that could be eliminated, though, for example to the extent that the step of confirming that the treatment composition exhibits the predetermined property is carried out for purposes of feedback control, e.g. to allow diversion of treatment composition that may not exhibit the predetermined property.

[0007] Accordingly, a need exists for improved methods for continuously inactivating a virus during manufacture of a protein.

BRIEF SUMMARY

[0008] There is provided a method for continuously inactivating a virus during manufacture of a protein. The method includes a step of (1) combining, at a single predetermined volumetric ratio, (a) a composition including the protein, and (b) a composition including a virus-inactivation reagent, to obtain (c) a treatment composition having a predetermined property for inactivation of a virus. The method also includes a step of (2) transferring the treatment composition to a treatment vessel. The method also includes a step of (3) incubating the treatment composition in the treatment vessel at predetermined conditions. The method also includes a step of (4) subjecting the treatment composition to a post-treatment processing operation. In accordance with the method, the single predetermined volumetric ratio has been selected to ensure that the predetermined property of the treatment composition is maintained across a range of concentrations predicted for the protein in the composition including the protein. Also in accordance with the method, steps (1) to (3) are carried out (a) continuously and (b) without feedback control being exerted by either adjustment of the volumetric ratio or diversion of the treatment composition. Accordingly, in one aspect, there is provided a method for continuously inactivating a virus during manufacture of a protein, the method comprising the steps of: (1) combining, at a single predetermined volumetric ratio,

(a) a composition comprising the protein, and (b) a composition comprising a virus-inactivation reagent, to obtain (c) a treatment composition having a predetermined property for inactivation of a virus; (2) transferring the treatment composition to a treatment vessel; (3) incubating the treatment composition in the treatment vessel at predetermined conditions; and (4) subjecting the treatment composition to a post-treatment processing operation; wherein: (i) the single predetermined volumetric ratio has been selected to ensure that the predetermined property of the treatment composition is maintained across a range of concentrations predicted for the protein in the composition comprising the protein; and (ii) steps (1) to (3) are carried out (a) continuously and (b) without feedback control being exerted by either adjustment of the volumetric ratio or diversion of the treatment composition.

[0009] Without wishing to be bound by theory, it is believed that by selecting the single predetermined volumetric ratio to ensure that the predetermined property of the treatment

composition is maintained across a range of concentrations predicted for the protein in the composition including the protein, and by carrying out steps (1) to (3) continuously and without feedback control being exerted by either adjustment of the volumetric ratio or diversion of the treatment composition, inactivation of virus during manufacture of a protein can be carried out in a stable manner without need for confirming that the treatment composition exhibits the predetermined property as inactivation of the virus is being carried out, allowing elimination of a control burden associated with feedback control during the inactivation of the virus.

[0010] There is also provided a method for inactivating one or more viruses in a sample. The method includes continuously mixing the sample with one or more virus-inactivating reagents as the sample flows from a first unit operation to a second unit operation during a process for purifying a target molecule. In accordance with the method, the ratio of the one or more virus-inactivating reagents to the sample is determined independently of, or without, a feedback control mechanism. Accordingly, in another aspect, there is provided a method for inactivating one or more viruses in a sample, wherein the method comprises continuously mixing the sample with one or more virus inactivating reagents as the sample flows from a first unit operation to a second unit operation during a process for purifying a target molecule, wherein the ratio of the one or more virus inactivating reagents to the sample is determined independently of, or without, a feedback control mechanism.

[0011] Without wishing to be bound by theory, it also is believed that by continuously mixing a sample with one or more virus-inactivating reagents as the sample flows from a first unit operation to a second unit operation during a process for purifying a target molecule, in accordance with the principles and approaches disclosed herein, including that the ratio of the one or more virus-inactivating reagents to the sample is determined independently of, or without, a feedback control mechanism, that inactivation of the one or more viruses can be accomplished to an extent sufficient for purposes of manufacturing biopharmaceutical products, also allowing elimination of a control burden associated with feedback control during the inactivation of the one or more viruses.

[0011a] In another aspect, there is provided a protein made according to the method as defined herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] These and other features, aspects, and advantages of the claimed methods, apparatuses, and systems are better understood when the following detailed description is read with reference to the accompanying drawings, in which:

[0013] **FIG. 1** is a schematic view of an example treatment vessel **210** for use in a method for continuously inactivating a virus during manufacture of a protein, in which the example treatment vessel **210** has a linear shape;