Claims:

1. A method for increasing the percentage of monomer in a composition of recombinantly expressed antibody molecules characterised in that the antibody molecule comprises at least one Fv with specificity for an antigen of interest comprising one VH and one VL wherein said VH and VL are connected directly or indirectly via one or more linkers and are stabilised by a disulfide bond therebetween, said method comprises:

   a) a thermal conversion step of holding the composition comprising the antibody molecule at a temperature in the range 30 to 60°C for a period of at least 1 hour,
   b) wherein step a) is performed in the presence of a reducing agent or after treatment with a reducing agent.

2. A method according to claim 1, wherein the temperature is in the range 45 to 55°C, for example 50 to 55°C.

3. A method according to claim 3, wherein the temperature is 50°C

4. A method according to any one of claims 1 to 3, wherein the reducing agent is selected from the group comprising: glutathione (GSH), ethylsulfite, 2-mercaptoethanol (BME), 2-mercaptoethylamine (BMEA), cysteine-HCl and dithiothreitol (DTT).

5. A method according to claim 4, wherein the reducing agent is selected from 2-mercaptoethanol (BME) and 2-mercaptoethylamine (BMEA), in particular 2-mercaptoethylamine.

6. A method according to any one of claims 1 to 5, wherein the concentration of reducing agent is in the range 1mM to 100mM, for example 30 to 90mM, 60 to 90 mM or 70 to 80 mM.

7. A method according to any one of claims 1 to 6, wherein the period is in the range 1 to 70 hours, for example 3 to 10 hours, such as 4 to 6 hours, in particular 5 hours.

8. A method according to claim 7, wherein step a) is performed at a temperature in the range 45 to 55°C, for a period of 4 to 6 hours and in step b) the reducing agent is BMEA or BME and is at a concentration in the range 60 to 90mM.

9. A method according to claim 8, wherein step a) is performed at a temperature of 50°C, for a period of 5 hours and in step b) the reducing agent is BMEA or BME and is at a concentration 70 to 80mM, for example 75 mM.

10. A method according to any one of claims 1 to 9, wherein the reducing agent is employed in the presence of an amino acid.

11. A method according to claim 10, wherein the amino acid is selected from arginine, lysine and proline.

12. A method according claim 10 or claim 11, wherein the concentration of amino acid is in the range 0.01 to 1.0 M, for example 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 M.

13. A method according to any one of claims 1 to 12, wherein the antibody is at a concentration in the range 0.5g/L to 5g/L in the composition, for example 2 to 3 g/L.

14. A method according to any one of claims 1 to 13, wherein the thermal step is performed in the presence of concomitant stirring.

15. A method according to claim 14, wherein the stirring in the range 100 to 1200 rpm.

16. A method according to any one of claims 1 to 15, wherein reducing agent is added to the recombinant antibody composition before the temperature is raised to be in the range 40 to 60°C.

17. A method according to any one of claims 1 to 15, wherein reducing agent is added to the recombinant antibody composition after the temperature is in the 40 to 60°C.

18. A method according to any one of claims 1 to 17, comprising the further step of downstream purification.

19. A method according to claim 18, wherein downstream processing comprises the step chromatography.

20. A method according to claim 19, wherein the chromatography is hydrophobic interaction chromatography.

21. A method according to claim 19, wherein the chromatography is ion exchange chromatography.

22. A method according to any of claims 1 to 21, wherein the VH and VL which are connected directly or indirectly via one or more linkers and are stabilised by a disulfide bond therebetween, are a complementary VH/VL pair which form an antigen binding site.

23. A method according to any preceding claim, wherein the VH and VL are connected directly via a linker.

24. A method according to claim 23, wherein the antibody is selected from a dsscFv, a Fab-2xdsscFv, a Fab-dsscFv-dsFv, a Fab-dsscFv-sdAb, a Fab-dsscFv-scFv and a Fab-dsscFv.

25. A method according to any of claims 1 to 22, wherein each VH and VL comprise a linker which indirectly connect the VH and VL via a second antibody.

26. A method according to claim 25, wherein the antibody is a Fab-dsFv.

27. A method according to claim 26, wherein the antibody is a bispecific antibody fusion protein which binds human OX40 and human serum albumin comprising:

a heavy chain comprising, in sequence from the N-terminal, a first heavy chain variable domain (V_H1), a C_H1 domain and a second heavy chain variable domain (V_H2),

a light chain comprising, in sequence from the N-terminal, a first light chain variable domain (V_L1), a C_L domain and a second light chain variable domain (V_L2),

wherein said heavy and light chains are aligned such that V_H1 and V_L1 form a first antigen binding site and V_H2 and V_L2 form a second antigen binding site,

wherein the antigen bound by the first antigen binding site is human OX40 and the antigen bound by the second antigen binding site is human serum albumin.

28. A method according to claim 27, wherein the first variable domain of the heavy chain (V_H1) comprises the sequence given in SEQ ID NO:1 for CDR-H1, the sequence given in SEQ ID NO:2 for CDR-H2 and the sequence given in SEQ ID NO:3 for CDR-H3 and the first variable domain of the light chain (V_L1) comprises the sequence given in SEQ ID NO:4 for CDR-L1, the sequence given in SEQ ID NO:5 for CDR-L2 and the sequence given in SEQ ID NO:6 for CDR-L3,

wherein the second heavy chain variable domain (V_H2) has the sequence given in SEQ ID NO:11 and the second light chain variable domain (V_L2) has the sequence given in SEQ ID NO: 12 and

the second heavy chain variable domain (V_H2) and second light chain variable domain (V_L2) are linked by a disulfide bond.