CLAIMS

What is claimed is:

1. A method of manufacturing fractionated heparin, the method comprising:

dissolving heparin in a solvent to form a heparin solution; and

fractionating the heparin solution by tangential flow filtration using a fractionation membrane with a molecular weight cut off between about 3 kDa and about 12 kDa, thereby yielding fractionated heparin with a weight average molecular weight of about 20 kDa or greater,

wherein at least 50% of heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater.

2. The method of claim 1, wherein the heparin is USP heparin.

3. The method of any one of claims 1-2, wherein the solvent is a sodium chloride (NaCl) solution.

4. The method of claim 3, where the NaCl solution has a concentration of about 100 mM.

5. The method of any one of claims 1-4, wherein the molecular weight cut off of the fractionation membrane is about 10 kDa.

6. The method of any one of claims 1-5, wherein fractionating the heparin solution by tangential flow filtration comprises permeating at least some of the heparin solution through the fractionation membrane under an applied pressure to yield a retentate comprising the fractionated heparin.

7. The method of claim 6, wherein the applied pressure is about 29 psi to about 30 psi.

8. The method of any one of claims 6-7, wherein fractionating the heparin solution by tangential flow filtration further comprises adding an additional quantity of the solvent to maintain a volume of the retentate.

9. The method of any one of claims 1-8, further comprising filtering the heparin solution through a submicron membrane to sterilize the heparin solution.

10. The method of any one of claims 1-9, further comprising desalting the fractionated heparin.

11. The method of claim 10, wherein desalting the fractionated heparin comprises performing tangential flow filtration using a desalting membrane with a molecular weight cut off between about 1 kDa and about 5 kDa.

12. The method of claim 11, wherein the molecular weight cut off of the desalting membrane is about 3 kDa.

13. The method of any one of claims 1-12, further comprising drying the fractionated heparin.

14. The method of claim 13, wherein drying the fractionated heparin comprising lyophilizing the fractionated heparin.

15. The method of any one of claims 1-14, wherein the weight average molecular weight of the fractionated heparin is about 30 kDa or greater.

16. The method of claim 15, wherein the weight average molecular weight of the fractionated heparin is about 40 kDa or greater.

17. The method of any one of claims 1-16, wherein the at least 60% of the heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater.

18. The method of claim 17, wherein the at least 70% of the heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater.

19. The method of any one of claims 1-18, wherein the molecular weight cut off of the fractionation membrane is between about 8 kDa and about 12 kDa.

20. A method of manufacturing a high molecular weight (HMW) heparin, the method comprising:

dissolving a heparin salt in a salt solution to form a heparin solution;

sterilizing the heparin solution by filtering through a sterilization membrane having a pore size of about 0.2 μm, thereby yielding a sterilized heparin solution;

fractionating the sterilized heparin solution by tangential flow filtration using a fractionation membrane with a pore size of about 5 nm, thereby yielding fractionated heparin with a weight average molecular weight of about 20 kDa or greater, wherein at least 50% of heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater;

desalting the fractionated heparin by tangential flow filtration using a desalting membrane with a pore size of about 3 nm, thereby yielding desalted heparin; and

drying the desalted heparin by lyophilization to yield the HMW heparin.

21. The method of claim 20, wherein the heparin salt is selected from the group consisting of heparin sodium and heparin calcium.

22. The method of any one of claims 20-21, wherein the heparin salt is a USP heparin salt.

23. The method of any one of claims 20-22, wherein the salt solution is a sodium chloride (NaCl) solution.

24. The method of claim 23, where the NaCl solution has a concentration of about 100 mM.

25. The method of any one of claims 20-24, wherein the molecular weight cut off of the fractionation membrane is about 10 kDa.

26. The method of any one of claims 20-25, wherein fractionating the sterilized heparin solution by tangential flow filtration comprises permeating at least some of the sterilized heparin solution through the fractionation membrane under an applied pressure to yield a retentate comprising the fractionated heparin.

27. The method of claim 26, wherein the applied pressure is about 29 psi to about 30 psi.

28. The method of any one of claims 26-27, wherein fractionating the sterilized heparin solution by tangential flow filtration further comprises adding an additional quantity of the salt solution to maintain a volume of the retentate.

29. The method of any one of claims 20-28, wherein the molecular weight cut off of the desalting membrane is about 3 kDa.

30. The method of any one of claims 20-29, wherein the weight average molecular weight of the fractionated heparin is about 30 kDa or greater.

31. The method of claim 30, wherein the weight average molecular weight of the fractionated heparin is about 40 kDa or greater.

32. The method of any one of claims 20-31, wherein the at least 60% of the heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater.

33. The method of claim 32, wherein the at least 70% of the heparin chains in the fractionated heparin have a molecular weight of 20 kDa or greater.

34. The method of any one of claims 20-33, wherein fractionating the sterilized heparin solution by tangential flow filtration comprises permeating at least some of the sterilized heparin solution through the fractionation membrane under a transmembrane pressure of about 30 psi such that (1) heparin chains in the sterilized heparin having a molecular weight of less than 20 kDa permeate through the filtration membrane as a filtrate, and (2) heparin chains in the sterilized heparin having a molecular weight of 20 kDa or greater do not permeate the filtration membrane, thereby yielding the retentate comprising the fractionated heparin,

wherein the heparin salt comprises heparin sodium and the salt solution comprises sodium chloride (NaCl) solution in a concentration of about 100 mM.