Disclosed herein are systems and methods for high viscosity ultrafiltration/diafiltration (UF/DF) and SPTFF processes used in the purification of polypeptides. The systems and methods disclosed herein can include one or more purification processes followed by an SPTFF operation. The one or more purification processes can include ultrafiltration and diafiltration. The one or more purification processes can result in a pool having a viscosity of between about 5-40 cP, which can then be subjected to an SPTFF operation. The SPTFF operation can include using membranes in either or both of a serial and/or parallel configuration to produce a resulting pool having an operating viscosity of about 41-400 cP.

[0006] According to an aspect, there is disclosed a method for purifying a polypeptide from a polypeptide preparation, comprising the following steps in order: a) subjecting the polypeptide preparation to one or more purification processes and recovering a first resulting pool having a viscosity of about 5-40 cP; and b) subjecting the pool recovered from step a) to a single pass tangential flow filtration (SPTFF) operation and recovering a second resulting pool having an operating viscosity of about 41-400 cP, wherein, i) the operating temperature is about 15-55°C, and ii) the feed flux is about 5-50 $L/m^2/hr$ (LMH).

[0007] In some examples of the method, in step a) the viscosity of the first recovered pool is 10-35 cP.

[0008] In some examples of the method, in step b) the STPFF operation comprises use of a serial membrane configuration.

[0009] In some examples of the method, in step b) the STPFF operation comprises use of a parallel membrane configuration.

[0010] In some examples of the method, in step b) the SPTFF operation comprises use of both a serial membrane configuration and a parallel membrane configuration.

[0011] In some examples of the method, in step b) wherein the membrane configuration is any of 1:1:1, 1:1:1:1, 2:1:1, or 2:2:1:1.

[0012] In some examples of the method, in step b) the membrane configuration comprises at least one of 10 kD membranes and 30 kD membrane.

[0013] In some examples of the method, in step b) the membrane configuration comprises at least one of narrow channel membranes and wide channel membranes.

[0014] In some examples of the method, in step a) the polypeptide preparation is formulated in a viscosity-reducing excipient.

[0015] In some examples of the method, in step b) the operating temperature is about 15-50°C or about 30-50°C.

[0016] In some examples of the method, in step b) the feed flux is about 5-25 LMH or about 25-50 LMH.

[0017] In some examples of the method, the operating viscosity in step b) is about 200-400 cP or about 200-300cP.

[0018] In some examples of the method, in step b) the retentate pressure is about 5-20 psi.

[0019] In some examples of the method, the one or more purification processes of step a) comprises an ultrafiltration.

[0020] In some examples of the method, the one or more purification processes of step a) comprises at least two ultrafiltration operations.

[0021] In some examples of the method, the one or more purification processes of step a) comprises a diafiltration.

[0022] In some examples of the method, step a) comprises i) subjecting the polypeptide preparation to an ultrafiltration operation to a first target concentration, ii) subjecting the polypeptide preparation to a diafiltration operation for buffer exchange, and iii) subjecting the polypeptide preparation to a second ultrafiltration operation to a second target concentration and recovering the first resulting pool having a viscosity of 5-40cP.

[0023] In some examples of the method, the first target concentration is 5-80 g/L.

[0024] In some examples of the method, the buffer exchange is a 6-12x exchange.

[0025] In some examples of the method, the second target concentration is 100-150 g/L or 100-200 g/L.

[0026] In some examples of the method, the polypeptide preparation comprises the polypeptide and one or more impurities.

[0027] In some examples of the method, the one or more purification processes of step a) comprise at least one of: a harvest step, a sample conditioning step, a viral filtration step, a viral inactivation step, a chromatography polishing step, a chromatography capture step, a dilution step, a tangential flow depth filtration step, a depth filtration step, a diafiltration step, an ultrafiltration step, a guard filtration step, a precipitation step, and a flocculation step.

[0028] In some examples, the method further comprises: subjecting the second resulting pool to one or more subsequent purification processes, wherein the one or more subsequent

purification processes comprise at least one of: a viral filtration step, a viral inactivation step, a chromatography polishing step, a chromatography capture step, a dilution step, a sample conditioning step, a diafiltration step, a tangential flow depth filtration step, a depth filtration step, a sterile filtration step, and a guard filtration step.

[0029] According to an aspect, there is disclosed a system for purifying a polypeptide from a polypeptide preparation, the system configured to perform the following steps in order: a) subject the polypeptide preparation to one or more purification processes and recover a first resulting pool having a viscosity of about 5-40 cP; and b) subject the pool recovered from step a) to a single pass tangential flow filtration (SPTFF) operation and recover a second resulting pool having an operating viscosity of about 41-400 cP, wherein, i) the operating temperature is about 15-55°C, and ii) the feed flux is about 5-50 $L/m^2/hr$ (LMH).

[0030] In some examples of the system, in step a) the viscosity of the first recovered pool is 10-35 cP.

[0031] In some examples of the system, in step b) the STPFF operation comprises use of a serial membrane configuration.

[0032] In some examples of the system, in step b) the STPFF operation comprises use of a parallel membrane configuration.

[0033] In some examples of the system, in step b) the SPTFF operation comprises use of both a serial membrane configuration and a parallel membrane configuration.

[0034] In some examples of the system, in step b) wherein the membrane configuration is any of 1:1:1, 1:1:1:1, 2:1:1, or 2:2:1:1.

[0035] In some examples of the system, in step b) the membrane configuration comprises at least one of 10 kD membranes and 30 kD membrane.

[0036] In some examples of the system, in step b) the membrane configuration comprises at least one of narrow channel membranes and wide channel membranes.

[0037] In some examples of the system, in step a) the polypeptide preparation is formulated in a viscosity-reducing excipient.

[0038] In some examples of the system, in step b) the operating temperature is about 15-50°C or about 30-50°C.

[0039] In some examples of the system, in step b) the feed flux is about 5-25 LMH or about 25-50 LMH.

[0040] In some examples of the system, the operating viscosity in step b) is about 200-400 cP or about 200-300cP.

[0041] In some examples of the system, in step b) the retentate pressure is about 5-20 psi.

[0042] In some examples of the system, the one or more purification processes of step a) comprises an ultrafiltration.

[0043] In some examples of the system, the one or more purification processes of step a) comprises at least two ultrafiltration operations.

[0044] In some examples of the system, the one or more purification processes of step a) comprises a diafiltration.

[0045] In some examples of the system, in step a) the system is configured to: i) subject the polypeptide preparation to an ultrafiltration operation to a first target concentration, ii) subject the polypeptide preparation to a diafiltration operation for buffer exchange, and iii) subject the polypeptide preparation to a second ultrafiltration operation to a second target concentration and recover the first resulting pool having a viscosity of 5-40cP.

[0046] In some examples of the system, the first target concentration is 5-80 g/L.

[0047] In some examples of the system, the buffer exchange is a 6-12x exchange.

[0048] In some examples of the system, the second target concentration is 100-150 g/L or 100-200 g/L.

[0049] In some examples of the system, the polypeptide preparation comprises the polypeptide and one or more impurities.

[0050] In some examples of the system, the one or more purification processes of step a) comprise at least one of: a harvest step, a sample conditioning step, a viral filtration step, a viral inactivation step, a chromatography polishing step, a chromatography capture step, a dilution step, a tangential flow depth filtration step, a depth filtration step, a diafiltration step, an ultrafiltration step, a guard filtration step, a precipitation step, and a flocculation step.

[0051] In some examples of the system, the system is further configured to: subject the second resulting pool to one or more subsequent purification processes, wherein the one or more subsequent purification processes comprise at least one of: a viral filtration step, a viral inactivation step, a chromatography polishing step, a chromatography capture step, a dilution step, a sample conditioning step, a diafiltration step, a tangential flow depth filtration step, a depth filtration step, a sterile filtration step, and a guard filtration step.