PATENT APPLICATION

FORMULATIONS OF RECOMBINANT FURIN

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 61/492,712, filed June 2, 2011, the content of which is expressly incorporated herein by reference in its entirety for all purposes.

FIELD OF THE APPLICATION

[0002] This application generally relates to the field of protein formulations.

BACKGROUND OF THE INVENTION

[0003] The family of the proteolytic mammalian subtilisin-like proprotein convertases (SPC or PC) is homologous with bacterial subtilisins and yeast Kex2p. To date seven distinct members of the SPC family have been identified, including furin, PC1 (also known as PC3), PC2, PACE4, PC4, PC5 (also known as PC6), PC7 (LPC, PC8, or SPC7), each of which exhibits unique tissue distribution.

[0004] Furin, also termed PACE (paired basic amino acid cleavage enzyme) is ubiquitously expressed in all mammalian tissues and cell lines and is capable of processing a wide range of bioactive precursor proteins in the secretory pathway, including also hormones, growth factors, receptors, viral and bacterial proteins, and plasma proteins. It is a calcium-dependent serine endoprotease structurally arranged into several domains, namely a signal peptide, propeptide, catalytic domain, middle domain, (also termed homo-B or P-domain), the C-terminally located cysteine-rich domain, transmembrane domain and the cytoplasmic tail. The furin protease cleavage site comprises a recognition sequence which is characterized by the amino acid sequence Arg-X-Lys/Arg-Arg (Hosaka et al., J Biol Chem. 1991; 266:12127-30).

[0005] Furin belongs to the family of the pro-protein convertases and is dependent on calcium (Ca^{2+}). Furin specifically cleaves the C-terminal peptide bond of arginine within a specific

sequence, containing arginine at positions −1 and −4. This sequence can be found in numerous human proteins, showing that furin plays a major role in the maturation of a number of human pro-proteins. Accordingly, furin is a proprotein convertase that processes latent precursor proteins into their biologically active products. Furin is a calcium-dependent serine endoprotease that cleaves precursor proteins at their paired basic amino acid processing sites. One substrate for furin is von Willebrand Factor (vWF).

[0006] Furin (*e.g.*, rfurin) is capable of converting pro-VWF (pro-von Willebrand factor) into mature VWF by cleaving the Arg741-Ser742 peptide bond of VWF. This maturation step is part of, for example, a rVWF production process which provides a therapy for von Willebrand Disease Type B. The production of activated recombinant proteins is of high clinical and diagnostic importance. For example, active or mature proteins, like mature VWF, may be used to control blood coagulation.

[0007] Furin formulations, particularly recombinant furin (rfurin) formulations, often have low shelf life (less than 6 months) due to a loss of rfurin activity from protein degradation (often from self-cleavage of the furin protein). In addition, when used in certain production processes, such as production of mature vWF, rfurin formulations are diluted, often by 200-fold, and the diluted rfurin generally shows a disproportionate loss of activity. Accordingly, there is a need in the field for methods and formulations that stabilize furin (*e.g.*, rfurin) compositions, as well as methods for diluting concentrated furin (*e.g.*, rfurin) compositions without losing a substantial fraction of furin activity.

BRIEF SUMMARY OF THE INVENTION

[0008] The present disclosure fulfills these and other needs in the field of furin (*e.g.*, rfurin) formulation, storage, and manipulation, by providing methods and formulations for stabilizing furin (*e.g.*, rfurin compositions). These needs are met, at least in part, by the discovery that the addition of sugars, sugar alcohols, and/or non-ionic surfactants significantly increases the stability of furin (*e.g.*, rfurin) compositions during storage and mechanical stress.

[0009] Accordingly, the present invention provides highly stabilized furin formulations, particularly highly stabilized rfurin formulations that show increased stability under conditions

of high temperature, agitation, and varying pH as compared to the starting (control) furin formulations.

[0010] In one aspect, the present disclosure provides a stabilized aqueous composition of recombinant furin (rfurin), the composition comprising: from 8,000 U/mL to 500,000 U/mL rfurin; from 100 mM to 300 mM of a pharmaceutically acceptable salt; from 0.5 mM to 2 mM calcium; from 2% to 20% sugar or sugar alcohol; from 10 to 200 ppm non-ionic surfactant; from 10 to 200 mM buffering agent; and a pH from 5.5 to 7.5.

[0011] In one embodiment, the compositions provided above include 150 mM to 250 mM of a pharmaceutically acceptable salt. In another embodiment, the compositions provided above include 190±10 mM of a pharmaceutically acceptable salt. In another embodiment, the compositions provided above include 190 mM of a pharmaceutically acceptable salt.

[0012] In one embodiment of the compositions provided above, the pharmaceutically acceptable salt is sodium chloride. In another embodiment of the compositions provided above, the pharmaceutically acceptable salt is potassium chloride.

[0013] In one embodiment, the compositions provided above include 0.9±0.2 mM calcium. In another embodiment, the compositions provided above include 0.92 mM calcium.

[0014] In one embodiment, the compositions provided above include from 5% to 15% sugar or sugar alcohol. In another embodiment, the compositions provided above include 10±2% sugar or sugar alcohol. In another embodiment, the compositions provided above include 10% sugar or sugar alcohol.

[0015] In one embodiment of the compositions provided above, the sugar or sugar alcohol is selected from the group consisting of sucrose, trehalose, mannitol, and a combination thereof. In another embodiment of the compositions provided above, the sugar or sugar alcohol is trehalose. In another embodiment of the compositions provided above, the sugar or sugar alcohol is sucrose.

[0016] In one embodiment, the compositions provided above include from 10 ppm to 100 ppm non-ionic surfactant. In another embodiment, the compositions provided above include from 50

ppm to 100 ppm non-ionic surfactant. In another embodiment, the compositions provided above include 75 ppm non-ionic surfactant.

[0017] In one embodiment of the compositions provided above, the non-ionic surfactant is polysorbate-80.

[0018] In one embodiment, the compositions provided above include from 50 mM to 150 mM buffering agent. In another embodiment, the compositions provided above include 90±10 mM buffering agent. In another embodiment, the compositions provided above include 91 mM buffering agent.

[0019] In one embodiment of the compositions provided above, the buffering agent comprises acetate. In another embodiment of the compositions provided above, the buffering agent comprises HEPES. In another embodiment of the compositions provided above, the buffering agent comprises MES. In another embodiment of the compositions provided above, the buffering agent comprises acetate and HEPES.

[0020] In one embodiment, the compositions provided above include from 25 mM to 75 mM acetate and from 25 to 75 mM HEPES. In another embodiment, the compositions provided above include 45±5 mM acetate and 45±5 mM HEPES. In another embodiment, the compositions provided above include 45 mM acetate and 46 mM HEPES.

[0021] In one embodiment, the compositions provided above have a pH from 5.5 to 7.0. In another embodiment, the compositions provided above have a pH from 5.5 to 6.5. In another embodiment, the compositions provided above have a pH of 6.0±0.2. In another embodiment, the compositions provided above have a pH of 6.0.

[0022] In one embodiment of the compositions provided above, the composition has increased stability when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

[0023] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin activity when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

[0024] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin monomer content when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

[0025] In one embodiment of the compositions provided above, the composition has increased stability when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0026] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin activity when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0027] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin monomer content when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0028] In one embodiment of the compositions provided above, the composition has increased stability when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0029] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin activity when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0030] In one embodiment of the compositions provided above, the composition maintains a higher percentage of rfurin monomer content when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

[0031] In one aspect, the present disclosure provides a stabilized aqueous composition of recombinant furin (rfurin), the composition comprising: from 8,000 U/mL to 500,000 U/mL rfurin; 190 mM sodium chloride; 0.92 mM calcium; 10% trehalose; 75 ppm polysorbate 80; 45 mM acetic acid; 46 mM HEPES; and a pH from 5.5 to 7.5.

[0032] In one embodiment, the compositions provided above have a pH from 5.5 to 7.0. In another embodiment, the compositions provided above have a pH from 5.5 to 6.5. In another

embodiment, the compositions provided above have a pH of 6.0±0.2. In another embodiment, the compositions provided above have a pH of 6.0.

[0033] In one aspect, the present disclosure provides a method for diluting an aqueous rfurin composition, the method comprising adding a dilution buffer comprising from 10 ppm to 200 ppm of a non-ionic surfactant to the aqueous rfurin composition, thereby forming a diluted rfurin composition.

[0034] In one embodiment of the methods provided above, the dilution buffer comprises from 10 ppm to 100 ppm of a non-ionic surfactant. In another embodiment of the methods provided above, the dilution buffer comprises from 50 ppm to 100 ppm of a non-ionic surfactant. In another embodiment of the methods provided above, the dilution buffer comprises 75 ppm of a non-ionic surfactant.

[0035] In one embodiment of the methods provided above, the dilution buffer has a pH of from 5.5 to 7.5. In another embodiment of the methods provided above, the dilution buffer has a pH of from 5.5 to 6.5. In another embodiment of the methods provided above, the dilution buffer has a pH of 6.0±0.2. In another embodiment of the methods provided above, the dilution buffer has a pH of 6.0.

[0036] In one embodiment of the methods provided above, the diluted rfurin composition comprises at least 50% of rfurin activity present in the aqueous rfurin composition prior to dilution.

[0037] In one embodiment of the methods provided above, the diluted rfurin composition comprises at least 75% of rfurin activity present in the aqueous rfurin composition prior to dilution.

[0038] In one aspect, the present disclosure provides a highly stabilized formulation of recombinant furin (rfurin), said formulation comprising: 8,000 – 52,000 U/mL rfurin; 1 mM to 300 mM of a pharmaceutically acceptable salt; 0.1 mM to 2 mM calcium chloride; 1% to 20% sugar and/or sugar dihydrate; 50 to 100 ppm of a surfactant; and 1 mM to 100 mM of a carboxylic acid, a buffering agent in sufficient concentration for maintaining a pH of 4.0-7.0, or both said carboxylic acid and said buffering agent.

[0039] In one embodiment, the formulations provided above include 180-200 mM salt.

[0040] In one embodiment of the formulations provided above, the salt is sodium chloride.

[0041] In one embodiment, the formulations provided above include 0.5 - 1.0 mM calcium.

[0042] In one embodiment, the formulations provided above include 5-15% sugar or sugar dihydrate.

[0043] In one embodiment of the formulations provided above, the sugar or sugar dihydrate is selected from the group consisting of sucrose, trehalose, mannitol, and a combination thereof.

[0044] In one embodiment of the formulations provided above, the surfactant is polysorbate 80.

[0045] In one embodiment of the formulations provided above, the surfactant is present at a concentration of about 65 to about 85 ppm.

[0046] In one embodiment of the formulations provided above, the carboxylic acid is acetic acid.

[0047] In one embodiment of the formulations provided above, the carboxylic acid is in a concentration of 35-55 mM.

[0048] In one embodiment of the formulations provided above, the buffering agent is HEPES.

[0049] In one embodiment of the formulations provided above, the buffering agent is in a concentration of about 20 to about 100 mM.

[0050] In one embodiment of the formulations provided above, the formulation shows improved stability after storage at 37°C as compared to a formulation that does not contain a sugar or sugar dihydrate.

[0051] In one embodiment of the formulations provided above, the formulation is prepared by adding rfurin to a composition comprising 1% polysorbate 80, 500 mM HEPES; 400 mM acetic acid, 1 mM calcium chloride, and trehalose dihydrate powder, wherein said composition has a pH of 6.0 prior to addition to said rfurin.

[0052] In one aspect, the present disclosure provides a highly stabilized formulation of recombinant furin (rfurin), said formulation comprising: 8,000 – 57,000 U/mL rfurin; 190 mM sodium chloride; 0.92 mM calcium chloride; 10% w/w trehalose dihydrate; 75 ppm polysorbate 80; 45 mM acetic acid; and 46 mM HEPES.

[0053] In one aspect, the present disclosure provides a highly stabilized formulation of recombinant furin (rfurin) that includes: (a) 8,000 – 52,000 U/mL rfurin; (b) 1 mM to 300 mM of a pharmaceutically acceptable salt; (c) 0.1 mM to 2 mM calcium chloride; (d) 1% to 20% sugar and/or sugar dihydrate; (e) 50 to 100 ppm of a surfactant; and (f) 1 mM to 100 mM of a carboxylic acid or a buffering agent in sufficient concentration for maintaining a pH of 4.0-7.0 or both the carboxylic acid and the buffering agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0054] Figure 1. rFurin in the control formulation – a temperature study analyzed using the furin activity assay. rFurin samples in the control formulation were incubated at: room temperature, 37°C, or 45°C for up to seven days. The activities of rfurin samples are plotted against the number of days of incubation. Error bars are ± 1 standard deviation; n=4.

[0055] Figure 2. rFurin in the control formulation – a temperature study analyzed using SEC. The same samples as in FIG. 1 were analyzed using SEC. Relative rfurin peak heights are plotted against the number of days of incubation. The relative peak heights were calculated as the percentages of the rfurin peak height at time zero.

[0056] Figure 3. rFurin in the control formulation incubated at 37°C analyzed using SEC. rFurin samples in the control formulation were incubated at 37°C for seven days. Figure 3 shows an overlay of SEC absorption profiles at 280 nm of six time points. The same study as in FIG. 1.

[0057] Figure 4. rFurin in the control formulation incubated at room temperature and 37°C analyzed using Western Blotting. The same study as in FIG. 1. Lane: (1) MWM marker; (2) T = 0; (3) rfurin incubated at room temperature for 1 day; (4) rfurin incubated at room temperature for 2 days; (5) rfurin incubated at room temperature for 3 days; (6) rfurin incubated at room temperature for 7 days; (7) MWM marker; (8) rfurin incubated at 37°C for 1 day; (9) rfurin

incubated at 37°C for 2 days; (10) rfurin incubated at 37°C for 3 days; and (11) rfurin incubated at 37°C for 7 days.

[0058] Figure 5. rFurin in the control formulation – a freeze/thaw study analyzed using the furin activity assay. rFurin activity is plotted against the number of freeze/thaw cycles. Error bars are ± 1 standard deviation; n=4.

[0059] Figure 6. rFurin in the control formulation – a freeze/thaw study analyzed using SEC. rFurin peak heights are plotted against the number of freeze/thaw cycles.

[0060] Figure 7. rFurin in the control formulation – an agitation study analyzed using the activity assay. rFurin activity is plotted against the time of agitation. Error bars are ± 1 standard deviation; n=4.

[0061] Figure 8. rFurin in the control formulation – an agitation study analyzed using SEC. rFurin peak heights are plotted against the time of agitation.

[0062] Figure 9. Comparison of different lots of rfurin using Western Blotting. Various lots of rfurin were analyzed using Western Blotting. Production order is denoted alphabetically. Lane: (1) MWM marker; (2) furin reference; (3) 03-04-09 (lot 018342, 2 mL vial); (4) 03-08-09 (lot 018365, 2 mL vial); (5) 03-15-09 (lot 018366, 2 mL vial); (6) 03-01-09 (lot 018315, 2 mL vial); (7) 07-26-10 (lot X572, 200 mL bottle); (8) 03-06-09 (lot 018365, 200 mL bottle); (9) 08-01-10 (lot X576, 200 mL bottle); (10) 03-09-09 (lot 018366, 200 mL bottle); (11) MWM marker; (12) furin reference; (13) 08-03-10 (lot X577, 200 mL bottle); (14) 07-24-10 (lot X573, 200 mL bottle); (15) 07-30-10 (lot X575, 200 mL bottle); (16) 018346 (QC Stability at -80°C); (17) 018346 (QC Stability at -25°C); (18) 018315 (QC Stability at -80°C); and (19) 018315 (QC Stability at -25°C).

[0063] Figure 10. Impact of thawing method on rfurin activity analyzed using the furin activity assay. rFurin sample activities are shown as bars for various lots of rfurin thawed at either: 4°C (left) or room temperature (RT; right). Error bars are ± 1 standard deviation; n=4.

[0064] Figure 11. Effect of pH 5 and 5.5 on rfurin activity analyzed using the furin activity assay. rFurin samples were incubated at 37°C at either pH: 5.0, 5.5, or 6.0 (control formulation)

for up to seven days. The activities of rfurin samples are plotted against the number of days of incubation. Error bars are ± 1 standard deviation; n=4.

[0065] Figure 12. Effect of pH 5 and 5.5 on rfurin activity analyzed using SEC. rFurin samples were incubated at 37°C at either pH: 5.0, 5.5 or 6.0 (control formulation). Relative peak heights of rfurin are plotted against the number of days of incubation. The relative peak heights were calculated as the percentage of the rfurin peak height at time zero.

[0066] Figure 13. rFurin stability at 37°C in the control formulation analyzed using SEC. A rfurin sample in the control formulation was incubated for four days at 37°C. The overlay of 280 nm absorption profiles shows three time points: T=0, 1 day, and 4 days of incubation.

[0067] Figure 14. rFurin stability in MES pH 6.0 analyzed using SEC. A rfurin sample was spiked with MES (final C=100 mM, pH 6.0) and incubated for four days at 37°C. An overlay of 280 nm absorption profiles shows three time points: T=0, 1 day, and 4 days of incubation.

[0068] Figure 15. rFurin stability in HEPES pH 7.0 analyzed using SEC. A rfurin sample was spiked with HEPES (final C=100 mM, pH 7.0) and incubated for four days at 37°C. The overlay of 280 nm absorption profiles shows three time points: T=0, 1 day, and 4 days of incubation.

[0069] Figure 16. rFurin stability in HEPES pH 8.0 analyzed using SEC. A rfurin sample was spiked with HEPES (final C=100 mM, pH 8.0) and incubated for four days at 37°C. The overlay of 280 nm absorption profiles shows three time points: T=0, 1 day, and 4 days of incubation.

[0070] Figure 17. Effects of sucrose and polysorbate 80 additives on rfurin stability at 37 °C analyzed using SEC. The samples were incubated at 37°C for four days. Relative peak heights of rfurin are plotted against the time of incubation. The relative peak heights were calculated as the percentages of the rfurin peak height at time zero.

[0071] Figure 18. Effects of sucrose and polysorbate 80 on rfurin stability in the control formulation at 37°C analyzed using the furin activity assay. The relative activities of rfurin samples are plotted against the number of days of incubation to compare the following samples: control formulation without additives, control formulation plus 10% sucrose, and control formulation plus 10% sucrose plus 25 ppm polysorbate 80. The relative activity values were

calculated as the percentages of the furin activity at time zero. Error bars are ± 1 standard deviation=4.

[0072] Figure 19. Effects of sucrose and polysorbate 80 on rfurin stability in MES buffer at 37°C analyzed using the furin activity assay. The relative activities of rfurin samples are plotted against the number of days of incubation to compare the following samples: control formulation without additives, spiked with MES (final C=100 mM, pH 6.0), spiked with MES (final C=100 mM, pH 6. plus 10% sucrose, and spiked with MES (final C=100 mM, pH 6.0) plus 10% sucrose plus 25 ppm polysorbate 80. The relative activity values were calculated as the percentages of the furin activity at time zero. Error bars are ± 1 standard deviation; n=4.

[0073] Figure 20. Comparison of rfurin stability at 37°C in the control formulation to the formulation in MES buffer analyzed using the furin activity assay. The relative activities of rfurin samples are plotted against the number of days of incubation to compare the following samples: control formulation without additives, control formulation plus 10% sucrose, and spiked with MES (final C=100 mM, pH 6.0) plus 10% sucrose. The relative activity values were calculated as the percentages of the furin activity at time zero. Error bars are ± 1 standard deviation; n=4.

[0074] Figure 21. Comparison of rfurin stability at 37°C in sucrose to mannitol analyzed using the furin activity assay. All samples were spiked with HEPES/acetic acid, pH 6.0. The relative activities of rfurin samples are plotted against the number of days of incubation to compare the following samples: no additives, 10% sucrose, 10% mannitol, 10% sucrose plus 25 ppm of polysorbate 80, and 10% mannitol plus 25 ppm of polysorbate 80. The relative activity values were calculated as the percentages of the furin activity at time zero. Error bars are ± 1 standard deviation; n=4.

[0075] Figure 22. rFurin Stability at 37°C: sucrose vs. mannitol analyzed using SEC. The same samples as in FIG. 21 were analyzed using SEC. Relative rfurin peak heights are plotted against the time of incubation. The relative peak heights were calculated as the percentages of the rfurin peak height at time zero.

[0076] Figure 23. rFurin stability in trehalose after 5 days of incubation at 37°C analyzed by the furin activity assay. The effects of varied amounts of trehalose and polysorbate 80 on rfurin

stability at 37°C are examined using the furin activity assay. First, all samples were spiked with HEPES and acetic acid (final concentrations: HEPES – 50 mM, acetic acid – 50 mM, pH 6.0) then, either 10% sucrose or various amounts of trehalose and/or polysorbate 80 were added. A rfurin sample in the control formulation is also included. The data are sorted from the highest to lowest activity values after 5 days of incubation at 37°C (right bar in each pair). The left bar in each pair depicts furin activity values at time zero. Error bars are ± 1 standard deviation; n=4.

[0077] Figure 24. rFurin activity in trehalose after 5 days of incubation at 37°C. The same samples as in FIG. 23 are displayed after recalculation to show what percentage of each sample's initial activity remained after five days of incubation at 37°C. A rfurin sample in the control formulation is also included. Error bars are ± 1 standard deviation; n=4.

[0078] Figure 25. rFurin stability in trehalose after 5 days of incubation at 37°C analyzed using SEC. The same samples as in FIG. 24. The graph shows what percentage of each sample's initial rfurin peak remained after five days of incubation at 37°C. A rfurin sample in the control formulation is also included.

[0079] Figure 26. rFurin stability in trehalose after 5 days of incubation at 35°C analyzed using Western Blotting. The same samples as in FIG. 24. The samples are paired: first sample - time zero, second sample - incubated at 37°C for 5 days. Lanes: (1) MWM marker; (2) furin reference, (3) control; (4) control formulation, T=0; (5) control formulation, 5 days; (6) 10% sucrose, T = 0; (7) 10% sucrose, 5 days; (8) 2% trehalose, T=0; (9) 2% trehalose, 5 days; (10) 10% trehalose, T=0; (11) 10% trehalose, 5 days; (12) MWM marker; (13) furin reference; (14) control; (15) 5% trehalose, T=0; (16) 5% trehalose, 5 days; (17) 5% trehalose, + 10 ppm Tween80, T=0; (18) 5% trehalose, + 10 ppm Tween80, 5 days; (19) 5% trehalose, + 25 ppm Tween80, T=0; (20) 5% trehalose, + 25 ppm Tween80, 5 days; (21) 5% trehalose, + 100 ppm Tween80, T=0; and (22) 5% trehalose, + 100 ppm Tween80, 5 days.

[0080] Figure 27. Effect of the trehalose content on rfurin activity tested after 5 days of incubation at 37°C. The same experiment as in FIG. 24. First, all samples were spiked with HEPES and acetic acid (final concentrations: HEPES – 50 mM, acetic acid – 50 mM, pH 6.0) then, various amounts of trehalose were added. furin activity after five days of incubation at

37°C is plotted against the percentage of trehalose added to the samples. Error bars are ± 1 standard deviation; n=4.

[0081] Figure 28. Effect of the trehalose content on rfurin stability at 37 °C analyzed using SEC after 5 days of incubation. The same experiment as in FIG. 27. rFurin peak heights after five days of incubation at 37°C are plotted against the percentage of trehalose added to the samples.

[0082] Figure 29. Effect of polysorbate 80 content on rfurin activity tested after 5 days of incubation at 37°C. The same experiment as in FIG. 24. First, all samples were spiked with HEPES, acetic acid (final concentrations: HEPES – 50 mM, acetic acid – 50 mM, pH 6.0), and 5% trehalose then, various amounts of polysorbate 80 were added. furin activity after five days of incubation at 37°C is plotted against the amount of polysorbate 80 added to the samples. Error bars are ± 1 standard deviation; n=4.

[0083] Figure 30. Effect of Polysorbate 80 content on rfurin stability at 37 °C analyzed using SEC after 5 days of incubation. The same samples as in FIG. 29. rFurin peak heights after five days of incubation at 37°C are plotted against the amount of polysorbate 80 added to the samples.

[0084] Figure 31. rFurin in the highly stabilized formulation - agitation study analyzed using the furin activity assay. The rfurin samples in the highly stabilized formulation were spiked with various amount of polysorbate 80. The graph shows furin activity values before and after three hours of agitation. The data are sorted from the highest to the lowest activity. Error bars are ± 1 standard deviation; n=4. Left bars in each pair show activity at time 0, right bars in each pair show activity after agitation.

[0085] Figure 32. rFurin in the highly stabilized formulation - agitation study analyzed using SEC. The same experiment as in FIG. 31. The graph shows rfurin peak heights before and after three hours of agitation. The data are sorted from the highest to the lowest. Left bars in each pair show activity at time 0, right bars in each pair show activity after agitation.

[0086] Figure 33. rFurin in the highly stabilized formulation – effects of polysorbate content in an agitation study analyzed using the furin activity assay. The same samples as in FIG. 32.

furin activity after three hours of agitation is plotted against the content of polysorbate 80. Error bars are ± 1 standard deviation; n=4.

[0087] Figure 34. rFurin in the highly stabilized formulation – effect of polysorbate 80 in agitation study analyzed using SEC. The same samples as in FIG. 32. rFurin peak heights after three hours of agitation are plotted against the content of polysorbate 80.

[0088] Figure 35. rFurin in the control formulation – agitation study analyzed using SEC. The chromatogram shows an overlay of SEC absorption profiles at 280 nm comparing rfurin samples in the control formulation before and after three hours of agitation. The rfurin peak of the agitated sample is significantly smaller than the control sample. The absence of high molecular mass peaks in the agitated sample is observed (see paragraph 3.5.1 for explanation).

[0089] Figure 36. UV spectra of rfurin in the control formulation (the same samples as in FIG. 35). The UV spectrum of the rfurin sample after three hours of agitation shows a slanted and extremely elevated profile compared to the sample before agitation, which indicates the presence of a significant level of aggregates in the agitated sample.

[0090] Figure 37. UV spectra of the rfurin samples in the highly stabilized formulation without polysorbate 80. The UV spectrum of the rfurin sample after three hours of agitation shows an elevated profile compared to the sample before agitation, which indicates the presence of significant level of aggregates in the agitated sample.

[0091] Figure 38. rFurin in the highly stabilized Formulation without polysorbate 80 – an agitation study analyzed using SEC. The chromatogram shows an overlay of SEC absorption profiles at 280 nm comparing rfurin samples in the highly stabilized formulation without polysorbate 80 before and after three hours of agitation. The rfurin peak of the agitated sample is significantly smaller than the control sample. The absence of high molecular mass peaks is observed.

[0092] Figure 39. UV spectra of the rfurin samples in the highly stabilized formulation containing 10 ppm polysorbate 80. The UV spectrum of the rfurin sample after three hours of agitation shows a slightly elevated profile compared to the sample before agitation, which indicates the presence of aggregates in the agitated sample. The 'agitated' spectra is closer to the

'before agitated' spectra, relative to those seen in samples without polysorbate (Figs 36 and 37), which indicated that that the level of aggregation is less than that seen in samples without polysorbate.

[0093] Figure 40. UV spectra of the rfurin samples in the highly stabilized formulation containing 25 ppm polysorbate 80. The UV spectrum of the rfurin sample after three hours of agitation shows a slightly elevated profile compared to the sample before agitation, which indicates presence of a small amount of aggregates in the agitated sample.

[0094] Figure 41. UV spectra of the rfurin samples in the highly stabilized formulation containing 50 ppm polysorbate 80. The UV spectrum of the rfurin sample after three hours of agitation shows a very similar profile to the sample before agitation. Neither spectra is slanted or elevated, which indicates that neither sample contains significant amounts of large aggregates.

[0095] Figure 42. UV spectra of the rfurin samples in the highly stabilized formulation containing 100 ppm polysorbate 80. The UV spectrum of the rfurin sample after three hours of agitation shows a very similar profile to the sample before agitation. Neither spectra is slanted or elevated, which indicates that neither sample contains significant amounts of large aggregates.

[0096] Figure 43. rFurin in the highly stabilized Formulation – a freeze/thaw study analyzed using the furin activity assay. rFurin samples in the highly stabilized formulation were spiked with different amounts of polysorbate 80. The data show rfurin activity in the samples before and after 5 freeze/thaw cycles. The data are sorted from the highest to the lowest. Error bars are ± 1 standard deviation; n=4.

[0097] Figure 44. rFurin in the highly stabilized formulation – a freeze/thaw study analyzed using SEC. The same samples as in figure 43. The data show the rfurin peak heights before and after 5 freeze/thaw cycles. The data are sorted from the highest to the lowest.

[0098] Figure 45. rFurin in the highly stabilized Formulation – a freeze/thaw study analyzed using SEC. The same samples as in FIG. 44. The relative peak heights of rfurin are plotted against the number of freeze/thaw cycles. The relative peak heights were calculated as the percentages of the rfurin peak heights before the first freeze/thaw cycle.

[0099] Figure 46. rFurin stability in the highly stabilized formulation at 37°C analyzed using the furin activity assay. rFurin samples in either the control formulation or in the highly stabilized formulation were incubated at 37°C for 4 days. Error bars are ± 1 standard deviation; n=4.

[0100] Figure 47. rFurin stability in the highly stabilized formulation at 37°C analyzed using the furin activity assay. The same samples as in FIG. 46 recalculated. The relative activity of each sample was calculated as the percentage of its initial activity. Error bars are ± 1 standard deviation; n=4.

[0101] Figure 48. rFurin stability in the highly stabilized formulation at 37°C analyzed using SEC. The same samples as in FIG. 46. The relative peak height of rfurin for every sample was calculated as the percentage of its initial peak height. Error bars are ± 1 standard deviation; n=4.

[0102] Figure 49. Effect of temperature on the pH (B) and conductivity (A) of the highly stabilized formulation stock buffer (500 mM HEPES, 400 mM acetic acid, 1 mM $CaCl_2$, pH 6.0).

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0103] The present disclosure is based in part on the discovery that aqueous furin compositions can be stabilized against various chemical and mechanical stresses by the addition of sugars, sugar alcohols, and non-ionic surfactants. The aqueous furin compositions described herein are significantly more stable when stored at or above room temperature, as well as when subjected to mechanical stress, as compared to similar furin compositions lacking sugars, sugar alcohols, and non-ionic surfactants. The present disclosure is also based in part on the discovery that the addition of non-ionic surfactants to furin dilution buffers enables a greater recovery of furin activity when the enzyme is diluted to lower concentrations used during the manufacture of various recombinant biologics, such as VWF.

[0104] Advantageously, the studies described herein demonstrate that the addition of sugar or sugar alcohols to a furin composition enhances the stability of the composition when stored over a period of time. For example, it is shown herein that the inclusion of as little as 2% sugar or

sugar alcohol in an aqueous furin formulation can increase the stability of the composition by greater than 10%. It is further shown that inclusion of 10% sugar or sugar alcohol in an aqueous furin formulation can increase the stability of the composition by greater than 75%.

[0105] Advantageously, the studies described herein also demonstrate that the addition of non-ionic surfactant to a furin composition enhances the stability of the composition when subjected to mechanical stress. For example, it is shown herein that the inclusion of as little as 10 ppm of non-ionic surfactant in an aqueous furin formulation can increase the stability of the composition by greater than 75%.

[0106] Advantageously, the studies described herein also demonstrate that the inclusion of non-ionic surfactant to a furin dilution buffer increases the recovery of furin activity after dilution. For example, it is shown herein that the inclusion of 75 ppm of non-ionic surfactant in a furin dilution buffer increases the recovery of furin activity after dilution by 3- to 4-fold.

[0107] Accordingly, the present disclosure provides compositions of highly stabilized furin formulations. Although the majority of the discussion herein is in terms of highly stabilized formulations of recombinant furin (rfurin), it will be appreciated that any furin protein, including furin isolated from a subject or any derivatives or mutants of furin, can be included in the formulations of the present invention.

[0108] In one aspect, the present disclosure provides highly stabilized furin formulations that show improved stability over control formulations when assayed after subjecting the formulation to one or more stressors, including without limitation exposure of the formulations to a range of temperatures, to several freeze/thaw cycles, and/or to agitation. Improved stability is generally assessed by level of furin activity – for example, after storage at higher than ambient room temperature, a highly stabilized furin formulation will show a higher level of activity than a control formulation stored under identical conditions as compared to the activity of each prior to storage (*i.e.*, at time = 0). Methods for assessing the stability of a furin formulation are described herein.

[0109] In further aspects, the present disclosure provides methods for forming highly stabilized furin formulations of the present invention. Such methods include methods for

stabilizing a formulation of furin for storage, including frozen storage, storage at ambient room temperature or above, or lyophilization.

[0110] In yet other aspects, the present disclosure provides methods for diluting concentrated furin solutions that result in increased retention of furin activity after dilution. As compared to furin compositions diluted with solutions lacking non-ionic surfactant, aqueous compositions of furin diluted according to the methods provided herein retain 3- to 4-times more enzymatic activity.

II. Definitions

[0111] As used herein, the term "furin" refers to any protein or polypeptide with furin activity, particularly the ability to cleave the peptide bond between residues Arg-763 and Ser-764 of the pro-von Willebrand Factor (pro-VWF) polypeptide. In an exemplary embodiment, furin refers to a polypeptide comprising an amino acid sequence identical or highly identical to that of NP_002560.1 (human furin preproprotein). In an exemplary embodiment, furin refers to a polypeptide comprising an amino acid sequence identical or highly identical to amino acids 25-794 of NP_002560.1 (human furin proprotein). In an exemplary embodiment, furin refers to a polypeptide comprising an amino acid sequence identical or highly identical to amino acids 108-794 of NP_002560.1 (human mature furin protein). As used herein, furin polypeptides also include natural variants of furin with VWF cleaving activity, as well as modified furin constructs with VWF cleaving activity. As used herein, furin encompasses any natural variants, alternative sequences, isoforms or mutant proteins that retain some basal activity (for example, at least 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or more activity as compared to the activity of wild-type furin). Examples of furin mutations found in the human population include, without limitation, A43E, A43G, A43V, R50W, Y64C, L77P, R81C, E97A, E97V, V109M, V109L, R130W, A139V, P169T, N245S, E271K, Q339R, N407S, E457Q, R464W, K469R, S524Y, T536S, L570F, D624N, A642T, S685P, V728I, V735I, R745Q, P772L, and A793T. Furin polypeptides also include polypeptides containing post-translational modification. For example, it has been shown that furin is phosphorylated at residues S773 and S775 and predicted that furin is glycosylated at residues N387, N440, and N553.

[0112] In the context of the present disclosure, furin proteins include recombinant furin polypeptides as well as native furin polypeptides isolated from a source material (*e.g.*, tissue or blood). Furin polypeptides (recombinant and source purified) may be derived from any suitable organism, for example, a mammal such as a primate, human, monkey, rabbit, pig, rodent, mouse, rat, hamster, gerbil, canine, feline, and biologically active derivatives thereof. Mutant and variant furin polypeptides having VWF cleaving activity are also embraced, as are functional fragments, and fusion proteins comprising furin polypeptides. Furthermore, the furin polypeptides described herein may further comprise tags that facilitate purification, detection, or both. The furin polypeptides described herein may further be modified with a therapeutic moiety or a moiety suitable for imaging *in vitro* or *in vivo*.

[0113] Proteolytically active recombinant furin may be prepared by expression in cell culture (*e.g.*, mammalian cell culture). Non-limiting examples of expression and purification methods for preparing recombinant furin are described in WO 1991/06314, WO 1992/09698, U.S. Patent Nos. 6,210,929 and 6,596,526, as well as in U.S. Patent Application Publication Nos. 2009/0181423 and 2009/0304669, the contents of which are hereby incorporated by reference in their entireties for all purposes.

[0114] As used herein, "activity" refers to a functional activity or activities of furin or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, including participation in the proteolytic maturation of proprotein substrates and cleavage of test substrates such as Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1; AMC = 7-amino-4-methoxy coumarin). Substrates for furin include von Willebrand factor, proparathyroid hormone, transforming growth factor beta 1 precursor, proalbumin, pro-beta-secretase, membrane type-1 matrix metalloproteinase, and the beta subunit of pro-nerve growth factor. In one embodiment, one Unit (U) of furin activity is defined as the amount of furin that releases 1 pmol of AMC from Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1) per minute.

[0115] As used herein, the term "stability" (such as furin stability or furin formulation stability) is used in a structural context, *e.g.*, relating to the structural integrity of a protein, or in a functional context, *e.g.*, relating to a protein's ability to retain its function and/or activity over time. As will be appreciated, the protein under discussion may be contained within a formulation in accordance with the methods and compositions described herein, and the stability

of that protein refers to its stability in that formulation. In one embodiment, the stability of a furin composition is determined by measuring the furin activity of the composition. For example, by using a detectable furin substrate such as Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1; *e.g.*, ALX-260-040-M001 sold by Enzo Life Sciences), for example, in an assay as described in Malloy SS, *et al.*, J Biol Chem. 1992 Aug 15;267(23):16396-402, the content of which is hereby incorporated herein by reference in its entirety for all purposes. In one embodiment, the stability of furin composition formulated with sugar, sugar alcohol, and/or non-ionic surfactant, as described herein, is compared to a furin composition formulated without the sugar, sugar alcohol, and/or non-ionic surfactant.

[0116] As used herein, a "storage stable" aqueous furin composition refers to a furin polypeptide solution (*e.g.*, a rfurin polypeptide solution) that has been formulated to increase the stability of the protein in solution, for example by at least 10%, over a given storage time. In the context of the present disclosure, a furin polypeptide solution (*e.g.*, a rfurin polypeptide solution) can be made "storage stable" by the addition of a sugar, sugar alcohol, or non-ionic surfactant as a stabilizing agent. In some embodiments, the stability of the furin polypeptide in any given formulation can be measured, for example, by monitoring the formation of aggregates, loss of bulk enzymatic activity, or formation of degradation products, over a period of time. The absolute stability of a formulation, and the stabilizing effects of the sugar, sugar alcohol, or non-ionic surfactant, will vary dependent upon the particular composition being stabilized. In one embodiment, the stability of a furin composition is determined by measuring the furin activity of the composition. For example, by using a detectable furin substrate such as Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1; *e.g.*, ALX-260-040-M001 sold by Enzo Life Sciences), in an assay, for example, as described in Malloy SS, *et al.*, J Biol Chem. 1992 Aug 15;267(23):16396-402, the content of which is hereby incorporated by reference in its entirety for all purposes. In one embodiment, the stability of furin composition formulated with sugar, sugar alcohol, and/or non-ionic surfactant, as described herein, is compared to a furin composition formulated without the sugar, sugar alcohol, and/or non-ionic surfactant.

[0117] As used herein, "shelf-life" refers to the period of time a formulation maintains a predetermined level of stability at a predetermined temperature. In particular embodiments, the

predetermined temperature refers to frozen (*e.g.*, -80 °C, -25°C, 0°C), refrigerated (*e.g.*, 0° to 10°C), or room temperature (*e.g.*, 18°C to 32° C) storage.

[0118] As used herein, the term "time of stability" refers to the length of time a formulation is considered stable. For example, the time of stability for a formulation may refer to the length of time for which the level of protein aggregation and/or degradation in the formulation remains below a certain threshold (e.g., 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, etc.), and/or the length of time a formulation maintains biological activity above a certain threshold (e.g., 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, etc.) of the amount of activity present in the formulation at the start of the storage period.

[0119] In the context of the present disclosure, a storage stable aqueous composition of a furin polypeptide (*e.g.*, rfurin polypeptide) formulated with a sugar, sugar alcohol, and/or non-ionic surfactant will have a longer time of stability than a composition of the same furin polypeptide formulated without the sugar, sugar alcohol, and/or non-ionic surfactant. In some embodiments, a storage stable aqueous composition of a furin polypeptide, will have a time of stability that is, for example, at least 10% greater than the time of stability for the same composition formulated in the absence of the sugar, sugar alcohol, and/or non-ionic surfactant, or at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% greater, or at least 2 times greater, or at least 2.5 times, 3.0 times, 3.5 times, 4.0 times, 4.5 times, 5.0 times, 5.5 times, 6.0 times, 6.5 times, 7.0 times, 7.5 times, 8.0 times, 8.5 times, 9.0 times, 9.5 times, 10 times, or more times greater than the time of stability for the same composition formulated in the absence of the sugar, sugar alcohol, and/or non-ionic surfactant.

[0120] As used herein, "storage" means that a formulation is not immediately administered to a subject or utilized in a production process once prepared, but is kept for a period of time under particular conditions (e.g. particular temperature) prior to use. For example, a furin formulation can be kept for days, weeks, months or years, prior to administration to a subject under varied temperatures such as frozen (*e.g.*, -80 °C, -25°C, 0°C), refrigerated (*e.g.*, 0° to 10°C), or room temperature (*e.g.*, 18°C to 32° C). As will be appreciated, such formulations may be liquid or lyophilized formulations.

[0121] As used herein, the term "about" denotes an approximate range of plus or minus 10% from a specified value. For instance, the language "about 20%" encompasses a range of 18-22%.

[0122] As used herein, when referring to a concentration of an individual component of a composition, the phrases "no more than X" and "from 0 to X" are equivalent and refer to any concentration between and including 0 and X. For example, the phrases "a concentration of no more than 2%" and "a concentration of from 0% to 2%" are equivalent and include 0%, 1%, and 2%.

[0123] As used herein, when referring to a concentration of an individual component of a composition, the phrases "no less than X" refers to any concentration X or higher. For example, the phrase "a concentration of no less than 98%" includes 98%, 99%, and 100%.

[0124] As used herein, when referring to a concentration of an individual component of a composition, the phrases "between X and Y" and "from X to X" are equivalent and refer to any concentration between and including X and Y. For example, the phrases "a concentration of between 49% and 51%" and "a concentration of from 49% to 51%" are equivalent and include 49%, 50%, and 51%.

[0125] As used herein, a "sugar" refers to monosaccharides having the general formula $C_xH_{2y}O_y$ (linear) or $C_xH_{(2y-1)}O_y$ (cyclic), and disaccharides consisting of two monosaccharide units formed through a dehydration reaction. Monosaccharides can be classified by the number of carbon atoms they contain: diose (2), triose (3), tetrose (4), pentose (5), hexose (6), heptose (7), etc. Accordingly, as used herein, a C(X) sugar refers to a sugar containing X-number of carbon molecules. For example, a C(5) sugar refers to a pentose sugar, while a C(6) sugar refers to a hexose sugar. Non-limiting examples of sugars that may be used in the formulations provided herein include: diose sugar glycolaldehyde, triose sugars glyceraldehyde and dihydroxyacetone; tetrose sugars erythrose, threose, and erythrulose; pentose sugars arabinose, lyxose, ribose, xylose, ribulose, and xylulose; hexose sugars allose, altrose, glucose, mannose, gulose, idose, galactose, talose, psicose, fructose, sorbose, and tagatose; heptose sugars sedoheptulose, mannoheptulose, and L-glycero-D-manno-heptose; and all possible combinations of disaccharide sugars formed thereform, including without limitation sucrose, lactulose, lactose, maltose, trehalose, cellobiose, kojibiose, nigerose, isomaltose, β,β-trehalose, α,β-trehalose,

sophorose, laminaribiose, gentiobiose, turanose, maltulose, palatinose, gentiobiulose, mannobiose, melibiose, melibiulose, rutinose, rutinulose, and xylobiose.

[0126] As used herein, a "sugar alcohol" refers to a hydrogenated form of a mono- or disaccharide, whose carbonyl group has been reduced to form a primary or secondary hydroxyl. In one embodiment, the sugar alcohol has between about 4 and about 8 carbon atoms. Non-limiting examples of sugar alcohols that may be used in formulations provided herein include glycol, glycerol, erythritol, threitol, ribitol, fucitol, iditol, volmitol, isomalt, maltitol, lactitol, mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol.

[0127] As used herein, a "pharmaceutically acceptable salt" refers to a salt that is safe for administration to a subject (*e.g.*, a human) in a drug formulation. The selection and use of pharmaceutically acceptable salts is well known in the art, for example, *see* Stahl and Wermuth, Pharmaceutical Salts: Properties, Selection, and Use, 2nd Revised edition, Wiley, Hoboken, New Jersey. In certain embodiments, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof.

[0128] As used herein, the term "non-ionic surfactant" refers to a surface active agent that is non-ionized under physiologically relevant conditions. Non-limiting examples of non-ionic surfactants useful for the stabilized aqueous furin compositions provided herein include: non-ionic water soluble mono-, di-, and tri-glycerides (*e.g.*, propylene glycol dicarpylate/dicaprate (*e.g.* MIGLYOL® 840), medium chain mono- and diglycerides (*e.g.* CAPMUL® and IMWITOR® 72), medium-chain triglycerides (*e.g.* caprylic and capric triglycerides such as LAVRAFAC, MIGLYOL® 810 or 812, CRODAMOL® GTCC-PN, and SOFTISON 378), long chain monoglycerides (*e.g.* glyceryl monooleates such as PECEOL®, and glyceryl monolinoleates such as MAISINE®), polyoxyl castor oil (*e.g.* macrogolglycerol ricinoleate, macrogolglycerol hydroxystearate, macrogol cetostearyl ether)); non-ionic water soluble mono- and di-fatty acid esters of polyethyelene glycol; non-ionic water soluble sorbitan fatty acid esters (*e.g.*, sorbitan monolaurates such as polyoxyethylene (20) sorbitan monolaurate (TWEEN 20) and sorbitan monolaurate (SPAN 20); sorbitan monopalmitates such as polyoxyethylene (20) sorbitan monopalmitates (TWEEN 40) and sorbitan monopalmitate (SPAN 40); sorbitan monostearates such as polyoxyethylene (20) sorbitan monostearate (TWEEN 60) and sorbitan monostearate (SPAN 60); sorbitan monooleates such as polyoxyethylene (20) sorbitan

monooleate (TWEEN 80) and sorbitan monooleate (SPAN 80); sorbitane trioleates such as sorbitane trioleate (SPAN 85); and sorbitan tristearates such as sorbitan tristearate (SPAN65)); polyglycolyzed glycerides (*e.g.*, lauroyl macrogol-6 glycerides (Labrafil® M2130CS); d-α-tocopheryl polyethyleneglycol 1000 succinate (TPGS), poyethyleneglycol 660 12-hydroxystearate (SOLUTOL® HS 15), polyoxyl oleate and stearate (e.g. PEG 400 monostearate and PEG 1750 monostearate)); non-ionic water soluble triblock copolymers (e.g. poly(ethyleneoxide)/poly-(propyleneoxide)/poly(ethyleneoxide) triblock copolymers such as methyl-oxirane polymer with oxirane BHT (PLURONIC® F-127)).

[0129] In one embodiment, storage stable compositions of furin (*e.g.*, rfurin) are provided which contain a non-ionic surfactant selected from a non-ionic water soluble monoglyceride, a non-ionic water soluble diglyceride, a non-ionic water soluble triglyceride, a non-ionic water soluble monofatty acid esters of polyethyelene glycol, a non-ionic water soluble difatty acid esters of polyethyelene glycol, a non-ionic water soluble sorbitan fatty acid ester, a non-ionic polyglycolyzed glyceride, a non-ionic water soluble triblock copolymer, and a combination thereof.

[0130] As used herein, the term "biologically active derivative," when used in the context of furin polypeptide, also embraces polypeptides obtained via recombinant DNA technology. This may include any method known in the art for (i) the production of recombinant DNA by genetic engineering, *e.g.*, via reverse transcription of RNA and/or amplification of DNA, (ii) introducing recombinant DNA into prokaryotic or eukaryotic cells by transfection, *e.g.*, via electroporation or microinjection, (iii) cultivating said transformed cells, *e.g.*, in a continuous or batch-wise manner, (iv) expressing furin protein, *e.g.*, constitutively or upon induction, and (v) isolating said furin protein, *e.g.*, from the culture medium or by harvesting the transformed cells, in order to (vi) obtain substantially purified recombinant furin protein, *e.g.*, via ion exchange chromatography, size exclusion chromatography, affinity chromatography, hydrophobic interaction chromatography, and the like. The term "biologically active derivative" includes also chimeric molecules such as *e.g.*, a furin protein, or functional fragment thereof, in combination with a second polypeptide, *e.g.*, an immunoglobulin Fc domain or an albumin domain, in order to improve the biological/pharmacological properties such as *e.g.*, half life of the furin protein in the circulation system of a mammal, particularly a human.

[0131] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a buffering agent" refers to one agent or mixtures of such agents, and reference to "the method" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

[0132] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing devices, compositions, formulations and methodologies which are described in the publication and which might be used in connection with the presently described invention.

[0133] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[0134] As used herein, "BDS" refers to "Bulk Drug Substance."

III. Stabilized Aqueous Compositions of Recombinant furin

[0135] I n one aspect, the present disclosure provides stabilized aqueous formulations of furin, *e.g.*, rfurin. The following embodiments are based in part on the discovery that inclusion of a sugar, sugar alcohol, and/or non-ionic surfactant stabilizes aqueous furin compositions, as compared to compositions lacking the sugar, sugar alcohol, and/or non-ionic surfactant.

[0136] As will be recognized by one of skill in the art, furin compositions (*e.g.*, rfurin compositions) formulated according to the embodiments provided herein may contain, in addition to the components explicitly disclosed, counter ions contributed by the inclusion of

solution components or pH modifying agents, for example, sodium or potassium contributed from an acetate salt, sodium hydroxide, or potassium hydroxide or chloride contributed by calcium chloride or hydrochloric acid. In the context of the present disclosure, a storage stable furin composition (*e.g.*, rfurin) consisting of or consisting essentially of a given formulation may further comprise one or more counter ion, as necessitated by the formulation process at a particular pH.

[0137] In one embodiment, a storage stable furin composition (*e.g.*, rfurin composition) provided herein will be stabilized at room temperature (*i.e.*, between 18°C and 32°C) for a period of time. For example, in one embodiment, a storage stable, aqueous immunoglobulin composition will be stable when stored at room temperature for at least 4 days. In other embodiments, the composition will be stabile at room temperature for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, or more days. In other embodiments, the composition will be stable for at least 1 month. In yet other embodiments, the composition will be stable for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In certain embodiments, room temperature refers to between 20°C and 30°C, between 21°C and 29°C, between 22°C and 28°C, between 23°C and 27°C, between 24°C and 26°C, or about 25°C. In a specific embodiment, the composition will be stable for an extended period of time when stored at a temperature between 20°C and 25°C.

[0138] In one embodiment, a storage stable furin composition (*e.g.*, rfurin composition) provided herein will be stabilized at refrigerated temperature (*i.e.*, between 2°C and 10°C) for a period of time. For example, in one embodiment, a storage stable, aqueous immunoglobulin composition will be stable when stored at refrigerated temperature for at least 4 days. In other embodiments, the composition will be stabile at refrigerated temperature for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, or more days. In other embodiments, the composition will be stable for at least 1 month. In yet other embodiments, the composition will be stable for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In a specific embodiment, the composition will be stable for an extended period of time when stored at a temperature between 2°C and 8°C.

[0139] In one embodiment, a storage stable furin composition (*e.g.*, rfurin composition) provided herein will be stabilized at elevated temperature (*i.e.*, between 32°C and 42°C) for a period of time. For example, in one embodiment, a storage stable, aqueous immunoglobulin composition will be stable when stored at elevated temperature for at least 4 days. In other embodiments, the composition will be stabile at elevated temperature for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, or more days. In other embodiments, the composition will be stable for at least 1 month. In yet other embodiments, the composition will be stable for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In a specific embodiment, the composition will be stable for an extended period of time when stored at a temperature between 35°C and 40°C.

[0140] In one embodiment, a stored furin composition is considered storage stable as long as the composition maintains at least 40% of the furin activity present at the start of the storage period (*e.g.*, at time = 0). In another embodiment, a stored composition is considered stable as long as the composition maintains at least 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the furin activity present at the start of the storage period (*e.g.*, at time = 0). In one embodiment, furin activity is measures in an assay as described in Malloy SS, *et al.*, J Biol Chem. 1992 Aug 15;267(23):16396-402.

[0141] In one embodiment, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 10% more furin activity after storage for a period of time, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent. In other embodiments, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or a greater percentage more furin activity after storage for a period of time, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent.

[0142] In one embodiment, a stored furin composition is considered stable as long as the percentage of furin present in an aggregated state remains no more than 50%. In other

embodiments, a stored furin composition is considered stable as long as the percentage of furin present in an aggregated state remains no more than 45%, 40%, 35%, 30%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less.

[0143] In one embodiment, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 10% less furin present in an aggregated state after storage for a period of time, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent. In other embodiments, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or a greater percentage less furin present in an aggregated state after storage for a period of time, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent.

[0144] In one embodiment, a stored furin composition is considered stable as long as the composition maintains at least 40% of the starting furin activity (*e.g.*, at time = 0) after being subjected to mechanical stress. In another embodiment, a stored composition is considered stable as long as the composition maintains 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the starting furin activity (*e.g.*, at time = 0) after being subjected to mechanical stress. In a specific embodiment, the mechanical stress is agitation (*e.g.*, shaking).

[0145] In one embodiment, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 10% more furin activity after being subjected to mechanical stress, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent. In other embodiments, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or a greater percentage more furin activity after being subjected to mechanical stress, as compared to a furin composition not

containing the stabilizing agent or containing a lower amount of the stabilizing agent. In a specific embodiment, the mechanical stress is agitation (*e.g.*, shaking).

[0146] In one embodiment, a stored furin composition is considered stable as long as the percentage of furin present in an aggregated state remains no more than 50% after being subjected to mechanical stress. In other embodiments, a stored furin composition is considered stable as long as the percentage of furin present in an aggregated state remains no more than 45%, 40%, 35%, 30%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less after being subjected to mechanical stress. In a specific embodiment, the mechanical stress is agitation (*e.g.*, shaking).

[0147] In one embodiment, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 10% less furin present in an aggregated state after being subjected to mechanical stress, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent. In other embodiments, a furin composition is considered to have been stabilized by the addition of a stabilizing agent (*e.g.*, a sugar, sugar alcohol, or non-ionic surfactant) when the composition contains at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or a greater percentage less furin present in an aggregated state after being subjected to mechanical stress, as compared to a furin composition not containing the stabilizing agent or containing a lower amount of the stabilizing agent. In a specific embodiment, the mechanical stress is agitation (*e.g.*, shaking).

[0148] While the furin (*e.g.*, rfurin) formulations described in this application can be lyophilized and reconstituted in the indicated concentrations, it will be appreciated that these preparations can also be reconstituted in more dilute form. For example, a preparation according the present disclosure which is lyophilized and/or normally reconstituted in 2 mL of solution can also be reconstituted in a larger volume of diluent, such as 5 mL. Likewise, lyophilized furin (*e.g.*, rfurin) formulations can also be reconstituted in more concentrated form. For example, a preparation according the present disclosure which is lyophilized and/or normally reconstituted in 2 ml of solution can also be reconstituted in a smaller volume, such as 1 mL.

[0149] Advantageously, in one aspect, the highly stabilized furin (*e.g.*, rfurin) formulations of the present invention are combined with a diluent that confers increased furin recovery when the resultant composition is used in a production method, for example, in the maturation of rVWF (also referred to herein as an "rVWF maturation method"). Maturation of pro-von Willebrand factor (vWF) to its active form requires proteolytic processing after a pair of dibasic amino acids (- Lys-Arg-) at residue 763. It has been shown that vWF is preferentially processed by the paired dibasic amino acid-cleaving enzyme furin. Production processes for vWF thus include the use of furin, preferably in a highly stabilized formulation. In a further aspect, the highly stabilized formulation in this diluent increases furin activity recovery in the rVWF maturation step by three to four times compared to control formulations placed in control diluents.

[0150] In certain aspects, the highly stabilized formulations of the invention have a shelf life of at least 6 months. As will be appreciated, this shelf life may be at frozen temperatures (*i.e.*, -80°C, -25°C, 0°C), refrigerated (0°C to 10°C), or room temperature (20°C to 32°C) in liquid or lyophilized form. I n further aspects, the highly stabilized formulations of the invention have a shelf life of at least 12, 18, 24, 30, 36, 42, 48, 54, or 60 months.

[0151] In further aspects and in accordance with the above, shelf life is determined by a percent activity remaining after storage at any of the above temperatures for any of the above periods of time. In certain embodiments, shelf life means that the formulation retains at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 100% of furin activity as measured by any of the assays described herein or known in the art as compared to activity prior to storage for any of the above amounts of time at any of the above temperatures.

[0152] In one aspect, a highly stabilized formulation of furin (*e.g.*, rfurin) in accordance with the present disclosure includes: (a) 8,000 U/mL – 57,000 U/mL furin (*e.g.*, rfurin); (b) 190 mM sodium chloride; (c) 0.92 mM calcium chloride; (d) 10% w/w trehalose dihydrate; (e) 75 ppm polysorbate 80; (f) 45 mM acetic acid; and (g) 46 mM HEPES.

[0153] In certain aspects, highly stabilized formulations of the present disclosure include the following components: 47 mM HEPES, 46 mM acetic acid, 195 mM sodium chloride, 0.094 mM calcium chloride, 0.0075 % polysorbate 80, 10% w/w trehalose dihydrate, pH 6.0.

[0154] In further aspects, highly stabilized formulations of furin, including rfurin, in accordance with the present disclosure include (a) about 5,500 U/mL to 55,000 U/mL; 6,000 U/mL to 50,000 U/mL; 6,500 U/mL to 45,000 U/mL; 7,000 U/mL to 40,000 U/mL; 7,500 U/mL to 35,000 U/mL; 8,000 U/mL to 30,000 U/mL; 8,500 U/mL to 25,000 U/mL; 9,000 U/mL to 20,000 U/mL; 9,500 U/mL to 15,000 U/mL; or 10,000 U/mL furin; (b) about 100 mM to 300 mM, 110 mM to 280 mM, 120 mM to 260 mM, 130 mM to 240 mM, 140 mM to 220 mM, 150 mM to 200 mM, or 160 mM to 180 mM sodium chloride; (c) about 0.5 mM to 9 mM, 1 mM to 8 mM, 1.5 mM to 7 mM, 2 mM to 6 mM, 2.5 mM to 5 mM, or 3 mM to 4.5 mM calcium chloride; (d) about 0.5% to 19%, 1% to 18%, 1.5% to 17%, 2.0% to 16%, 2.5% to 15%, 3.0% to 14%, 3.5% to 13%, 4.0% to 12%, 4.5% to 11%, 5.0% to 10%, 5.5% to 9%, or 6.0% to 8% trehalose dihydrate; (e) about 0.5 ppm to 140 ppm, 1.0 ppm to 130 ppm, 10 ppm to 120 ppm, 20 ppm to 110 ppm, 30 ppm to 100 ppm, 40 ppm to 95 ppm, 50 ppm to 90 ppm, 55 ppm to 85 ppm, 60 ppm to 80 ppm, or 70 ppm to 75 ppm polysorbate 80; (f) about 25 mM to 90 mM, 30 mM to 80 mM, 35 mM to 70 mM, 40 mM to 60 mM, or 45 mM to 50 mM acetic acid, and (g) 15 mM to 95 mM, 20 mM to 90 mM, 25 mM to 85 mM, 30 mM to 80 mM, 35 mM to 75 mM, 40 mM to 70 mM, 45 mM to 65 mM, or 50 mM to 60 mM HEPES.

[0155] In one aspect, the present disclosure provides a stabilized aqueous furin composition (*e.g.*, rfurin) comprising: furin (*e.g.*, rfurin), from 2% to 20% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, from 50 mM to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 10 mM calcium, a buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar is a pentose or hexose sugar.

[0156] In one embodiment, a stabilized aqueous furin composition (*e.g.*, rfurin) comprises: furin (*e.g.*, rfurin), from 100 mM to 300 mM of a pharmaceutically acceptable salt; from 0.5 mM to 2 mM calcium; from 2% to 20% of a sugar or sugar alcohol; from 100 to 200 ppm of a non-ionic surfactant; from 10 to 200 mM buffering agent; and a pH from 5.5 to 7.5. In a specific embodiment, the sugar is a pentose or hexose sugar.

[0157] In a specific embodiment, highly stabilized formulations of the invention include the following components: 47 mM HEPES, 46 mM acetic acid, 195 mM sodium chloride, 0.094 mM calcium chloride, 0.0075 % polysorbate 80, 10% w/w trehalose dihydrate, pH 6.0.

[0158] In another specific embodiment, a highly stabilized formulation of furin (*e.g.*, rfurin) in accordance with the present invention includes: (a) 8,000 – 57,000 U/mL rfurin; (b) 190 mM sodium chloride; (c) 0.92 mM calcium chloride; (d) 10% w/w trehalose dihydrate; (e) 75 ppm polysorbate 80; (f) 45 mM acetic acid; and (g) 46 mM HEPES.

A. Stabilizing Agents

[0159] Advantageously, it was found that the inclusion of sugars, sugar alcohols, and non-ionic surfactants stabilizes aqueous furin (*e.g.*, rfurin) compositions. These effects are demonstrated in the examples provided herein. For example, the addition of these agents increases furin activity retention upon liquid storage, reduces aggregation of furin polypeptides upon liquid storage, reduces the degradation of furin polypeptides upon liquid storage, reduces the loss of furin activity upon agitation of an aqueous furin composition, and reduces aggregation caused by agitation of an aqueous furin composition.

[0160] Accordingly, in one embodiment, the present disclosure provides an aqueous furin composition (*e.g.*, a rfurin composition) comprising from 2% to 20% sugar or sugar alcohol and from 10 ppm to 200 ppm non-ionic surfactant. In another embodiment, the composition comprises from 2% to 10% sugar or sugar alcohol and from 10 ppm to 100 ppm non-ionic surfactant. In another embodiment, the composition comprises 10±2% sugar or sugar alcohol and 75±25 ppm non-ionic surfactant. In a specific embodiment, the composition comprises 10% sugar or sugar alcohol and 75 ppm non-ionic surfactant. In yet other embodiments, the composition comprises a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9.

Table 1. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

Non-Ionic Surfactant (ppm) \ Sugar or Sugar Alcohol (%)	2%-20%	2%-17.5%	2%-15%	2%-12.5%	2%-10%	2%-9%	2%-8%	2%-7%
10-200	Var. 1	Var. 86	Var. 171	Var. 256	Var. 341	Var. 426	Var. 511	Var. 596
10-175	Var. 2	Var. 87	Var. 172	Var. 257	Var. 342	Var. 427	Var. 512	Var. 597
10-150	Var. 3	Var. 88	Var. 173	Var. 258	Var. 343	Var. 428	Var. 513	Var. 598
10-125	Var. 4	Var. 89	Var. 174	Var. 259	Var. 344	Var. 429	Var. 514	Var. 599
10-100	Var. 5	Var. 90	Var. 175	Var. 260	Var. 345	Var. 430	Var. 515	Var. 600
10-90	Var. 6	Var. 91	Var. 176	Var. 261	Var. 346	Var. 431	Var. 516	Var. 601
10-80	Var. 7	Var. 92	Var. 177	Var. 262	Var. 347	Var. 432	Var. 517	Var. 602

10-75	Var. 8	Var. 93	Var. 178	Var. 263	Var. 348	Var. 433	Var. 518	Var. 603
10-70	Var. 9	Var. 94	Var. 179	Var. 264	Var. 349	Var. 434	Var. 519	Var. 604
10-60	Var. 10	Var. 95	Var. 180	Var. 265	Var. 350	Var. 435	Var. 520	Var. 605
10-50	Var. 11	Var. 96	Var. 181	Var. 266	Var. 351	Var. 436	Var. 521	Var. 606
10-25	Var. 12	Var. 97	Var. 182	Var. 267	Var. 352	Var. 437	Var. 522	Var. 607
25-200	Var. 13	Var. 98	Var. 183	Var. 268	Var. 353	Var. 438	Var. 523	Var. 608
25-175	Var. 14	Var. 99	Var. 184	Var. 269	Var. 354	Var. 439	Var. 524	Var. 609
25-150	Var. 15	Var. 100	Var. 185	Var. 270	Var. 355	Var. 440	Var. 525	Var. 610
25-125	Var. 16	Var. 101	Var. 186	Var. 271	Var. 356	Var. 441	Var. 526	Var. 611
25-100	Var. 17	Var. 102	Var. 187	Var. 272	Var. 357	Var. 442	Var. 527	Var. 612
25-90	Var. 18	Var. 103	Var. 188	Var. 273	Var. 358	Var. 443	Var. 528	Var. 613
25-80	Var. 19	Var. 104	Var. 189	Var. 274	Var. 359	Var. 444	Var. 529	Var. 614
25-70	Var. 20	Var. 105	Var. 190	Var. 275	Var. 360	Var. 445	Var. 530	Var. 615
25-60	Var. 21	Var. 106	Var. 191	Var. 276	Var. 361	Var. 446	Var. 531	Var. 616
25-50	Var. 22	Var. 107	Var. 192	Var. 277	Var. 362	Var. 447	Var. 532	Var. 617
50-200	Var. 23	Var. 108	Var. 193	Var. 278	Var. 363	Var. 448	Var. 533	Var. 618
50-175	Var. 24	Var. 109	Var. 194	Var. 279	Var. 364	Var. 449	Var. 534	Var. 619
50-150	Var. 25	Var. 110	Var. 195	Var. 280	Var. 365	Var. 450	Var. 535	Var. 620
50-125	Var. 26	Var. 111	Var. 196	Var. 281	Var. 366	Var. 451	Var. 536	Var. 621
50-90	Var. 27	Var. 112	Var. 197	Var. 282	Var. 367	Var. 452	Var. 537	Var. 622
50-80	Var. 28	Var. 113	Var. 198	Var. 283	Var. 368	Var. 453	Var. 538	Var. 623
75-200	Var. 29	Var. 114	Var. 199	Var. 284	Var. 369	Var. 454	Var. 539	Var. 624
75-175	Var. 30	Var. 115	Var. 200	Var. 285	Var. 370	Var. 455	Var. 540	Var. 625
75-150	Var. 31	Var. 116	Var. 201	Var. 286	Var. 371	Var. 456	Var. 541	Var. 626
100-200	Var. 32	Var. 117	Var. 202	Var. 287	Var. 372	Var. 457	Var. 542	Var. 627
100-175	Var. 33	Var. 118	Var. 203	Var. 288	Var. 373	Var. 458	Var. 543	Var. 628
50±25	Var. 34	Var. 119	Var. 204	Var. 289	Var. 374	Var. 459	Var. 544	Var. 629
60±25	Var. 35	Var. 120	Var. 205	Var. 290	Var. 375	Var. 460	Var. 545	Var. 630
70±25	Var. 36	Var. 121	Var. 206	Var. 291	Var. 376	Var. 461	Var. 546	Var. 631
75±25	Var. 37	Var. 122	Var. 207	Var. 292	Var. 377	Var. 462	Var. 547	Var. 632
80±25	Var. 38	Var. 123	Var. 208	Var. 293	Var. 378	Var. 463	Var. 548	Var. 633
90±25	Var. 39	Var. 124	Var. 209	Var. 294	Var. 379	Var. 464	Var. 549	Var. 634
100±25	Var. 40	Var. 125	Var. 210	Var. 295	Var. 380	Var. 465	Var. 550	Var. 635
125±25	Var. 41	Var. 126	Var. 211	Var. 296	Var. 381	Var. 466	Var. 551	Var. 636
150±25	Var. 42	Var. 127	Var. 212	Var. 297	Var. 382	Var. 467	Var. 552	Var. 637
175±25	Var. 43	Var. 128	Var. 213	Var. 298	Var. 383	Var. 468	Var. 553	Var. 638
30±10	Var. 44	Var. 129	Var. 214	Var. 299	Var. 384	Var. 469	Var. 554	Var. 639
40±10	Var. 45	Var. 130	Var. 215	Var. 300	Var. 385	Var. 470	Var. 555	Var. 640
50±10	Var. 46	Var. 131	Var. 216	Var. 301	Var. 386	Var. 471	Var. 556	Var. 641
60±10	Var. 47	Var. 132	Var. 217	Var. 302	Var. 387	Var. 472	Var. 557	Var. 642
70±10	Var. 48	Var. 133	Var. 218	Var. 303	Var. 388	Var. 473	Var. 558	Var. 643
75±10	Var. 49	Var. 134	Var. 219	Var. 304	Var. 389	Var. 474	Var. 559	Var. 644
80±10	Var. 50	Var. 135	Var. 220	Var. 305	Var. 390	Var. 475	Var. 560	Var. 645

90±10	Var. 51	Var. 136	Var. 221	Var. 306	Var. 391	Var. 476	Var. 561	Var. 646
100±10	Var. 52	Var. 137	Var. 222	Var. 307	Var. 392	Var. 477	Var. 562	Var. 647
110±10	Var. 53	Var. 138	Var. 223	Var. 308	Var. 393	Var. 478	Var. 563	Var. 648
120±10	Var. 54	Var. 139	Var. 224	Var. 309	Var. 394	Var. 479	Var. 564	Var. 649
125±10	Var. 55	Var. 140	Var. 225	Var. 310	Var. 395	Var. 480	Var. 565	Var. 650
130±10	Var. 56	Var. 141	Var. 226	Var. 311	Var. 396	Var. 481	Var. 566	Var. 651
140±10	Var. 57	Var. 142	Var. 227	Var. 312	Var. 397	Var. 482	Var. 567	Var. 652
150±10	Var. 58	Var. 143	Var. 228	Var. 313	Var. 398	Var. 483	Var. 568	Var. 653
160±10	Var. 59	Var. 144	Var. 229	Var. 314	Var. 399	Var. 484	Var. 569	Var. 654
170±10	Var. 60	Var. 145	Var. 230	Var. 315	Var. 400	Var. 485	Var. 570	Var. 655
175±10	Var. 61	Var. 146	Var. 231	Var. 316	Var. 401	Var. 486	Var. 571	Var. 656
180±10	Var. 62	Var. 147	Var. 232	Var. 317	Var. 402	Var. 487	Var. 572	Var. 657
190±10	Var. 63	Var. 148	Var. 233	Var. 318	Var. 403	Var. 488	Var. 573	Var. 658
25	Var. 64	Var. 149	Var. 234	Var. 319	Var. 404	Var. 489	Var. 574	Var. 659
30	Var. 65	Var. 150	Var. 235	Var. 320	Var. 405	Var. 490	Var. 575	Var. 660
40	Var. 66	Var. 151	Var. 236	Var. 321	Var. 406	Var. 491	Var. 576	Var. 661
50	Var. 67	Var. 152	Var. 237	Var. 322	Var. 407	Var. 492	Var. 577	Var. 662
60	Var. 68	Var. 153	Var. 238	Var. 323	Var. 408	Var. 493	Var. 578	Var. 663
70	Var. 69	Var. 154	Var. 239	Var. 324	Var. 409	Var. 494	Var. 579	Var. 664
75	Var. 70	Var. 155	Var. 240	Var. 325	Var. 410	Var. 495	Var. 580	Var. 665
80	Var. 71	Var. 156	Var. 241	Var. 326	Var. 411	Var. 496	Var. 581	Var. 666
90	Var. 72	Var. 157	Var. 242	Var. 327	Var. 412	Var. 497	Var. 582	Var. 667
100	Var. 73	Var. 158	Var. 243	Var. 328	Var. 413	Var. 498	Var. 583	Var. 668
110	Var. 74	Var. 159	Var. 244	Var. 329	Var. 414	Var. 499	Var. 584	Var. 669
120	Var. 75	Var. 160	Var. 245	Var. 330	Var. 415	Var. 500	Var. 585	Var. 670
125	Var. 76	Var. 161	Var. 246	Var. 331	Var. 416	Var. 501	Var. 586	Var. 671
130	Var. 77	Var. 162	Var. 247	Var. 332	Var. 417	Var. 502	Var. 587	Var. 672
140	Var. 78	Var. 163	Var. 248	Var. 333	Var. 418	Var. 503	Var. 588	Var. 673
150	Var. 79	Var. 164	Var. 249	Var. 334	Var. 419	Var. 504	Var. 589	Var. 674
160	Var. 80	Var. 165	Var. 250	Var. 335	Var. 420	Var. 505	Var. 590	Var. 675
170	Var. 81	Var. 166	Var. 251	Var. 336	Var. 421	Var. 506	Var. 591	Var. 676
175	Var. 82	Var. 167	Var. 252	Var. 337	Var. 422	Var. 507	Var. 592	Var. 677
180	Var. 83	Var. 168	Var. 253	Var. 338	Var. 423	Var. 508	Var. 593	Var. 678
190	Var. 84	Var. 169	Var. 254	Var. 339	Var. 424	Var. 509	Var. 594	Var. 679
200	Var. 85	Var. 170	Var. 255	Var. 340	Var. 425	Var. 510	Var. 595	Var. 680

Var. = Variation

Table 2. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

		Sugar or Sugar Alcohol (%)							
		5%-20%	5%-17.5%	5%-15%	5%-12.5%	5%-10%	7.5%-20%	7.5%-17.5%	7.5%-15%
Non-Ionic Surfactan	10-200	Var. 681	Var. 766	Var. 851	Var. 936	Var. 1021	Var. 1106	Var. 1191	Var. 1276
	10-175	Var. 682	Var. 767	Var. 852	Var. 937	Var. 1022	Var. 1107	Var. 1192	Var. 1277
	10-150	Var. 683	Var. 768	Var. 853	Var. 938	Var. 1023	Var. 1108	Var. 1193	Var. 1278

10-125	Var. 684	Var. 769	Var. 854	Var. 939	Var. 1024	Var. 1109	Var. 1194	Var. 1279
10-100	Var. 685	Var. 770	Var. 855	Var. 940	Var. 1025	Var. 1110	Var. 1195	Var. 1280
10-90	Var. 686	Var. 771	Var. 856	Var. 941	Var. 1026	Var. 1111	Var. 1196	Var. 1281
10-80	Var. 687	Var. 772	Var. 857	Var. 942	Var. 1027	Var. 1112	Var. 1197	Var. 1282
10-75	Var. 688	Var. 773	Var. 858	Var. 943	Var. 1028	Var. 1113	Var. 1198	Var. 1283
10-70	Var. 689	Var. 774	Var. 859	Var. 944	Var. 1029	Var. 1114	Var. 1199	Var. 1284
10-60	Var. 690	Var. 775	Var. 860	Var. 945	Var. 1030	Var. 1115	Var. 1200	Var. 1285
10-50	Var. 691	Var. 776	Var. 861	Var. 946	Var. 1031	Var. 1116	Var. 1201	Var. 1286
10-25	Var. 692	Var. 777	Var. 862	Var. 947	Var. 1032	Var. 1117	Var. 1202	Var. 1287
25-200	Var. 693	Var. 778	Var. 863	Var. 948	Var. 1033	Var. 1118	Var. 1203	Var. 1288
25-175	Var. 694	Var. 779	Var. 864	Var. 949	Var. 1034	Var. 1119	Var. 1204	Var. 1289
25-150	Var. 695	Var. 780	Var. 865	Var. 950	Var. 1035	Var. 1120	Var. 1205	Var. 1290
25-125	Var. 696	Var. 781	Var. 866	Var. 951	Var. 1036	Var. 1121	Var. 1206	Var. 1291
25-100	Var. 697	Var. 782	Var. 867	Var. 952	Var. 1037	Var. 1122	Var. 1207	Var. 1292
25-90	Var. 698	Var. 783	Var. 868	Var. 953	Var. 1038	Var. 1123	Var. 1208	Var. 1293
25-80	Var. 699	Var. 784	Var. 869	Var. 954	Var. 1039	Var. 1124	Var. 1209	Var. 1294
25-70	Var. 700	Var. 785	Var. 870	Var. 955	Var. 1040	Var. 1125	Var. 1210	Var. 1295
25-60	Var. 701	Var. 786	Var. 871	Var. 956	Var. 1041	Var. 1126	Var. 1211	Var. 1296
25-50	Var. 702	Var. 787	Var. 872	Var. 957	Var. 1042	Var. 1127	Var. 1212	Var. 1297
50-200	Var. 703	Var. 788	Var. 873	Var. 958	Var. 1043	Var. 1128	Var. 1213	Var. 1298
50-175	Var. 704	Var. 789	Var. 874	Var. 959	Var. 1044	Var. 1129	Var. 1214	Var. 1299
50-150	Var. 705	Var. 790	Var. 875	Var. 960	Var. 1045	Var. 1130	Var. 1215	Var. 1300
50-125	Var. 706	Var. 791	Var. 876	Var. 961	Var. 1046	Var. 1131	Var. 1216	Var. 1301
50-90	Var. 707	Var. 792	Var. 877	Var. 962	Var. 1047	Var. 1132	Var. 1217	Var. 1302
50-80	Var. 708	Var. 793	Var. 878	Var. 963	Var. 1048	Var. 1133	Var. 1218	Var. 1303
75-200	Var. 709	Var. 794	Var. 879	Var. 964	Var. 1049	Var. 1134	Var. 1219	Var. 1304
75-175	Var. 710	Var. 795	Var. 880	Var. 965	Var. 1050	Var. 1135	Var. 1220	Var. 1305
75-150	Var. 711	Var. 796	Var. 881	Var. 966	Var. 1051	Var. 1136	Var. 1221	Var. 1306
100-200	Var. 712	Var. 797	Var. 882	Var. 967	Var. 1052	Var. 1137	Var. 1222	Var. 1307
100-175	Var. 713	Var. 798	Var. 883	Var. 968	Var. 1053	Var. 1138	Var. 1223	Var. 1308
50±25	Var. 714	Var. 799	Var. 884	Var. 969	Var. 1054	Var. 1139	Var. 1224	Var. 1309
60±25	Var. 715	Var. 800	Var. 885	Var. 970	Var. 1055	Var. 1140	Var. 1225	Var. 1310
70±25	Var. 716	Var. 801	Var. 886	Var. 971	Var. 1056	Var. 1141	Var. 1226	Var. 1311
75±25	Var. 717	Var. 802	Var. 887	Var. 972	Var. 1057	Var. 1142	Var. 1227	Var. 1312
80±25	Var. 718	Var. 803	Var. 888	Var. 973	Var. 1058	Var. 1143	Var. 1228	Var. 1313
90±25	Var. 719	Var. 804	Var. 889	Var. 974	Var. 1059	Var. 1144	Var. 1229	Var. 1314
100±25	Var. 720	Var. 805	Var. 890	Var. 975	Var. 1060	Var. 1145	Var. 1230	Var. 1315
125±25	Var. 721	Var. 806	Var. 891	Var. 976	Var. 1061	Var. 1146	Var. 1231	Var. 1316
150±25	Var. 722	Var. 807	Var. 892	Var. 977	Var. 1062	Var. 1147	Var. 1232	Var. 1317
175±25	Var. 723	Var. 808	Var. 893	Var. 978	Var. 1063	Var. 1148	Var. 1233	Var. 1318
30±10	Var. 724	Var. 809	Var. 894	Var. 979	Var. 1064	Var. 1149	Var. 1234	Var. 1319
40±10	Var. 725	Var. 810	Var. 895	Var. 980	Var. 1065	Var. 1150	Var. 1235	Var. 1320
50±10	Var. 726	Var. 811	Var. 896	Var. 981	Var. 1066	Var. 1151	Var. 1236	Var. 1321

60±10	Var. 727	Var. 812	Var. 897	Var. 982	Var. 1067	Var. 1152	Var. 1237	Var. 1322
70±10	Var. 728	Var. 813	Var. 898	Var. 983	Var. 1068	Var. 1153	Var. 1238	Var. 1323
75±10	Var. 729	Var. 814	Var. 899	Var. 984	Var. 1069	Var. 1154	Var. 1239	Var. 1324
80±10	Var. 730	Var. 815	Var. 900	Var. 985	Var. 1070	Var. 1155	Var. 1240	Var. 1325
90±10	Var. 731	Var. 816	Var. 901	Var. 986	Var. 1071	Var. 1156	Var. 1241	Var. 1326
100±10	Var. 732	Var. 817	Var. 902	Var. 987	Var. 1072	Var. 1157	Var. 1242	Var. 1327
110±10	Var. 733	Var. 818	Var. 903	Var. 988	Var. 1073	Var. 1158	Var. 1243	Var. 1328
120±10	Var. 734	Var. 819	Var. 904	Var. 989	Var. 1074	Var. 1159	Var. 1244	Var. 1329
125±10	Var. 735	Var. 820	Var. 905	Var. 990	Var. 1075	Var. 1160	Var. 1245	Var. 1330
130±10	Var. 736	Var. 821	Var. 906	Var. 991	Var. 1076	Var. 1161	Var. 1246	Var. 1331
140±10	Var. 737	Var. 822	Var. 907	Var. 992	Var. 1077	Var. 1162	Var. 1247	Var. 1332
150±10	Var. 738	Var. 823	Var. 908	Var. 993	Var. 1078	Var. 1163	Var. 1248	Var. 1333
160±10	Var. 739	Var. 824	Var. 909	Var. 994	Var. 1079	Var. 1164	Var. 1249	Var. 1334
170±10	Var. 740	Var. 825	Var. 910	Var. 995	Var. 1080	Var. 1165	Var. 1250	Var. 1335
175±10	Var. 741	Var. 826	Var. 911	Var. 996	Var. 1081	Var. 1166	Var. 1251	Var. 1336
180±10	Var. 742	Var. 827	Var. 912	Var. 997	Var. 1082	Var. 1167	Var. 1252	Var. 1337
190±10	Var. 743	Var. 828	Var. 913	Var. 998	Var. 1083	Var. 1168	Var. 1253	Var. 1338
25	Var. 744	Var. 829	Var. 914	Var. 999	Var. 1084	Var. 1169	Var. 1254	Var. 1339
30	Var. 745	Var. 830	Var. 915	Var. 1000	Var. 1085	Var. 1170	Var. 1255	Var. 1340
40	Var. 746	Var. 831	Var. 916	Var. 1001	Var. 1086	Var. 1171	Var. 1256	Var. 1341
50	Var. 747	Var. 832	Var. 917	Var. 1002	Var. 1087	Var. 1172	Var. 1257	Var. 1342
60	Var. 748	Var. 833	Var. 918	Var. 1003	Var. 1088	Var. 1173	Var. 1258	Var. 1343
70	Var. 749	Var. 834	Var. 919	Var. 1004	Var. 1089	Var. 1174	Var. 1259	Var. 1344
75	Var. 750	Var. 835	Var. 920	Var. 1005	Var. 1090	Var. 1175	Var. 1260	Var. 1345
80	Var. 751	Var. 836	Var. 921	Var. 1006	Var. 1091	Var. 1176	Var. 1261	Var. 1346
90	Var. 752	Var. 837	Var. 922	Var. 1007	Var. 1092	Var. 1177	Var. 1262	Var. 1347
100	Var. 753	Var. 838	Var. 923	Var. 1008	Var. 1093	Var. 1178	Var. 1263	Var. 1348
110	Var. 754	Var. 839	Var. 924	Var. 1009	Var. 1094	Var. 1179	Var. 1264	Var. 1349
120	Var. 755	Var. 840	Var. 925	Var. 1010	Var. 1095	Var. 1180	Var. 1265	Var. 1350
125	Var. 756	Var. 841	Var. 926	Var. 1011	Var. 1096	Var. 1181	Var. 1266	Var. 1351
130	Var. 757	Var. 842	Var. 927	Var. 1012	Var. 1097	Var. 1182	Var. 1267	Var. 1352
140	Var. 758	Var. 843	Var. 928	Var. 1013	Var. 1098	Var. 1183	Var. 1268	Var. 1353
150	Var. 759	Var. 844	Var. 929	Var. 1014	Var. 1099	Var. 1184	Var. 1269	Var. 1354
160	Var. 760	Var. 845	Var. 930	Var. 1015	Var. 1100	Var. 1185	Var. 1270	Var. 1355
170	Var. 761	Var. 846	Var. 931	Var. 1016	Var. 1101	Var. 1186	Var. 1271	Var. 1356
175	Var. 762	Var. 847	Var. 932	Var. 1017	Var. 1102	Var. 1187	Var. 1272	Var. 1357
180	Var. 763	Var. 848	Var. 933	Var. 1018	Var. 1103	Var. 1188	Var. 1273	Var. 1358
190	Var. 764	Var. 849	Var. 934	Var. 1019	Var. 1104	Var. 1189	Var. 1274	Var. 1359
200	Var. 765	Var. 850	Var. 935	Var. 1020	Var. 1105	Var. 1190	Var. 1275	Var. 1360

Var. = Variation

Table 3. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

Sugar or Sugar Alcohol (%)

Non-Ionic Surfactant (ppm)

	7.5%-12.5%	10%-20%	10%-17.5%	10%-15%	4±2%	5±2%	6±2%	7±2%
10-200	Var. 1361	Var. 1446	Var. 1531	Var. 1616	Var. 1701	Var. 1786	Var. 1871	Var. 1956
10-175	Var. 1362	Var. 1447	Var. 1532	Var. 1617	Var. 1702	Var. 1787	Var. 1872	Var. 1957
10-150	Var. 1363	Var. 1448	Var. 1533	Var. 1618	Var. 1703	Var. 1788	Var. 1873	Var. 1958
10-125	Var. 1364	Var. 1449	Var. 1534	Var. 1619	Var. 1704	Var. 1789	Var. 1874	Var. 1959
10-100	Var. 1365	Var. 1450	Var. 1535	Var. 1620	Var. 1705	Var. 1790	Var. 1875	Var. 1960
10-90	Var. 1366	Var. 1451	Var. 1536	Var. 1621	Var. 1706	Var. 1791	Var. 1876	Var. 1961
10-80	Var. 1367	Var. 1452	Var. 1537	Var. 1622	Var. 1707	Var. 1792	Var. 1877	Var. 1962
10-75	Var. 1368	Var. 1453	Var. 1538	Var. 1623	Var. 1708	Var. 1793	Var. 1878	Var. 1963
10-70	Var. 1369	Var. 1454	Var. 1539	Var. 1624	Var. 1709	Var. 1794	Var. 1879	Var. 1964
10-60	Var. 1370	Var. 1455	Var. 1540	Var. 1625	Var. 1710	Var. 1795	Var. 1880	Var. 1965
10-50	Var. 1371	Var. 1456	Var. 1541	Var. 1626	Var. 1711	Var. 1796	Var. 1881	Var. 1966
10-25	Var. 1372	Var. 1457	Var. 1542	Var. 1627	Var. 1712	Var. 1797	Var. 1882	Var. 1967
25-200	Var. 1373	Var. 1458	Var. 1543	Var. 1628	Var. 1713	Var. 1798	Var. 1883	Var. 1968
25-175	Var. 1374	Var. 1459	Var. 1544	Var. 1629	Var. 1714	Var. 1799	Var. 1884	Var. 1969
25-150	Var. 1375	Var. 1460	Var. 1545	Var. 1630	Var. 1715	Var. 1800	Var. 1885	Var. 1970
25-125	Var. 1376	Var. 1461	Var. 1546	Var. 1631	Var. 1716	Var. 1801	Var. 1886	Var. 1971
25-100	Var. 1377	Var. 1462	Var. 1547	Var. 1632	Var. 1717	Var. 1802	Var. 1887	Var. 1972
25-90	Var. 1378	Var. 1463	Var. 1548	Var. 1633	Var. 1718	Var. 1803	Var. 1888	Var. 1973
25-80	Var. 1379	Var. 1464	Var. 1549	Var. 1634	Var. 1719	Var. 1804	Var. 1889	Var. 1974
25-70	Var. 1380	Var. 1465	Var. 1550	Var. 1635	Var. 1720	Var. 1805	Var. 1890	Var. 1975
25-60	Var. 1381	Var. 1466	Var. 1551	Var. 1636	Var. 1721	Var. 1806	Var. 1891	Var. 1976
25-50	Var. 1382	Var. 1467	Var. 1552	Var. 1637	Var. 1722	Var. 1807	Var. 1892	Var. 1977
50-200	Var. 1383	Var. 1468	Var. 1553	Var. 1638	Var. 1723	Var. 1808	Var. 1893	Var. 1978
50-175	Var. 1384	Var. 1469	Var. 1554	Var. 1639	Var. 1724	Var. 1809	Var. 1894	Var. 1979
50-150	Var. 1385	Var. 1470	Var. 1555	Var. 1640	Var. 1725	Var. 1810	Var. 1895	Var. 1980
50-125	Var. 1386	Var. 1471	Var. 1556	Var. 1641	Var. 1726	Var. 1811	Var. 1896	Var. 1981
50-90	Var. 1387	Var. 1472	Var. 1557	Var. 1642	Var. 1727	Var. 1812	Var. 1897	Var. 1982
50-80	Var. 1388	Var. 1473	Var. 1558	Var. 1643	Var. 1728	Var. 1813	Var. 1898	Var. 1983
75-200	Var. 1389	Var. 1474	Var. 1559	Var. 1644	Var. 1729	Var. 1814	Var. 1899	Var. 1984
75-175	Var. 1390	Var. 1475	Var. 1560	Var. 1645	Var. 1730	Var. 1815	Var. 1900	Var. 1985
75-150	Var. 1391	Var. 1476	Var. 1561	Var. 1646	Var. 1731	Var. 1816	Var. 1901	Var. 1986
100-200	Var. 1392	Var. 1477	Var. 1562	Var. 1647	Var. 1732	Var. 1817	Var. 1902	Var. 1987
100-175	Var. 1393	Var. 1478	Var. 1563	Var. 1648	Var. 1733	Var. 1818	Var. 1903	Var. 1988
50±25	Var. 1394	Var. 1479	Var. 1564	Var. 1649	Var. 1734	Var. 1819	Var. 1904	Var. 1989
60±25	Var. 1395	Var. 1480	Var. 1565	Var. 1650	Var. 1735	Var. 1820	Var. 1905	Var. 1990
70±25	Var. 1396	Var. 1481	Var. 1566	Var. 1651	Var. 1736	Var. 1821	Var. 1906	Var. 1991
75±25	Var. 1397	Var. 1482	Var. 1567	Var. 1652	Var. 1737	Var. 1822	Var. 1907	Var. 1992
80±25	Var. 1398	Var. 1483	Var. 1568	Var. 1653	Var. 1738	Var. 1823	Var. 1908	Var. 1993
90±25	Var. 1399	Var. 1484	Var. 1569	Var. 1654	Var. 1739	Var. 1824	Var. 1909	Var. 1994
100±25	Var. 1400	Var. 1485	Var. 1570	Var. 1655	Var. 1740	Var. 1825	Var. 1910	Var. 1995
125±25	Var. 1401	Var. 1486	Var. 1571	Var. 1656	Var. 1741	Var. 1826	Var. 1911	Var. 1996
150±25	Var. 1402	Var. 1487	Var. 1572	Var. 1657	Var. 1742	Var. 1827	Var. 1912	Var. 1997

175±25	Var. 1403	Var. 1488	Var. 1573	Var. 1658	Var. 1743	Var. 1828	Var. 1913	Var. 1998
30±10	Var. 1404	Var. 1489	Var. 1574	Var. 1659	Var. 1744	Var. 1829	Var. 1914	Var. 1999
40±10	Var. 1405	Var. 1490	Var. 1575	Var. 1660	Var. 1745	Var. 1830	Var. 1915	Var. 2000
50±10	Var. 1406	Var. 1491	Var. 1576	Var. 1661	Var. 1746	Var. 1831	Var. 1916	Var. 2001
60±10	Var. 1407	Var. 1492	Var. 1577	Var. 1662	Var. 1747	Var. 1832	Var. 1917	Var. 2002
70±10	Var. 1408	Var. 1493	Var. 1578	Var. 1663	Var. 1748	Var. 1833	Var. 1918	Var. 2003
75±10	Var. 1409	Var. 1494	Var. 1579	Var. 1664	Var. 1749	Var. 1834	Var. 1919	Var. 2004
80±10	Var. 1410	Var. 1495	Var. 1580	Var. 1665	Var. 1750	Var. 1835	Var. 1920	Var. 2005
90±10	Var. 1411	Var. 1496	Var. 1581	Var. 1666	Var. 1751	Var. 1836	Var. 1921	Var. 2006
100±10	Var. 1412	Var. 1497	Var. 1582	Var. 1667	Var. 1752	Var. 1837	Var. 1922	Var. 2007
110±10	Var. 1413	Var. 1498	Var. 1583	Var. 1668	Var. 1753	Var. 1838	Var. 1923	Var. 2008
120±10	Var. 1414	Var. 1499	Var. 1584	Var. 1669	Var. 1754	Var. 1839	Var. 1924	Var. 2009
125±10	Var. 1415	Var. 1500	Var. 1585	Var. 1670	Var. 1755	Var. 1840	Var. 1925	Var. 2010
130±10	Var. 1416	Var. 1501	Var. 1586	Var. 1671	Var. 1756	Var. 1841	Var. 1926	Var. 2011
140±10	Var. 1417	Var. 1502	Var. 1587	Var. 1672	Var. 1757	Var. 1842	Var. 1927	Var. 2012
150±10	Var. 1418	Var. 1503	Var. 1588	Var. 1673	Var. 1758	Var. 1843	Var. 1928	Var. 2013
160±10	Var. 1419	Var. 1504	Var. 1589	Var. 1674	Var. 1759	Var. 1844	Var. 1929	Var. 2014
170±10	Var. 1420	Var. 1505	Var. 1590	Var. 1675	Var. 1760	Var. 1845	Var. 1930	Var. 2015
175±10	Var. 1421	Var. 1506	Var. 1591	Var. 1676	Var. 1761	Var. 1846	Var. 1931	Var. 2016
180±10	Var. 1422	Var. 1507	Var. 1592	Var. 1677	Var. 1762	Var. 1847	Var. 1932	Var. 2017
190±10	Var. 1423	Var. 1508	Var. 1593	Var. 1678	Var. 1763	Var. 1848	Var. 1933	Var. 2018
25	Var. 1424	Var. 1509	Var. 1594	Var. 1679	Var. 1764	Var. 1849	Var. 1934	Var. 2019
30	Var. 1425	Var. 1510	Var. 1595	Var. 1680	Var. 1765	Var. 1850	Var. 1935	Var. 2020
40	Var. 1426	Var. 1511	Var. 1596	Var. 1681	Var. 1766	Var. 1851	Var. 1936	Var. 2021
50	Var. 1427	Var. 1512	Var. 1597	Var. 1682	Var. 1767	Var. 1852	Var. 1937	Var. 2022
60	Var. 1428	Var. 1513	Var. 1598	Var. 1683	Var. 1768	Var. 1853	Var. 1938	Var. 2023
70	Var. 1429	Var. 1514	Var. 1599	Var. 1684	Var. 1769	Var. 1854	Var. 1939	Var. 2024
75	Var. 1430	Var. 1515	Var. 1600	Var. 1685	Var. 1770	Var. 1855	Var. 1940	Var. 2025
80	Var. 1431	Var. 1516	Var. 1601	Var. 1686	Var. 1771	Var. 1856	Var. 1941	Var. 2026
90	Var. 1432	Var. 1517	Var. 1602	Var. 1687	Var. 1772	Var. 1857	Var. 1942	Var. 2027
100	Var. 1433	Var. 1518	Var. 1603	Var. 1688	Var. 1773	Var. 1858	Var. 1943	Var. 2028
110	Var. 1434	Var. 1519	Var. 1604	Var. 1689	Var. 1774	Var. 1859	Var. 1944	Var. 2029
120	Var. 1435	Var. 1520	Var. 1605	Var. 1690	Var. 1775	Var. 1860	Var. 1945	Var. 2030
125	Var. 1436	Var. 1521	Var. 1606	Var. 1691	Var. 1776	Var. 1861	Var. 1946	Var. 2031
130	Var. 1437	Var. 1522	Var. 1607	Var. 1692	Var. 1777	Var. 1862	Var. 1947	Var. 2032
140	Var. 1438	Var. 1523	Var. 1608	Var. 1693	Var. 1778	Var. 1863	Var. 1948	Var. 2033
150	Var. 1439	Var. 1524	Var. 1609	Var. 1694	Var. 1779	Var. 1864	Var. 1949	Var. 2034
160	Var. 1440	Var. 1525	Var. 1610	Var. 1695	Var. 1780	Var. 1865	Var. 1950	Var. 2035
170	Var. 1441	Var. 1526	Var. 1611	Var. 1696	Var. 1781	Var. 1866	Var. 1951	Var. 2036
175	Var. 1442	Var. 1527	Var. 1612	Var. 1697	Var. 1782	Var. 1867	Var. 1952	Var. 2037
180	Var. 1443	Var. 1528	Var. 1613	Var. 1698	Var. 1783	Var. 1868	Var. 1953	Var. 2038
190	Var. 1444	Var. 1529	Var. 1614	Var. 1699	Var. 1784	Var. 1869	Var. 1954	Var. 2039
200	Var. 1445	Var. 1530	Var. 1615	Var. 1700	Var. 1785	Var. 1870	Var. 1955	Var. 2040

Var. = Variation

Table 4. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

Non-Ionic Surfactant (ppm) \ Sugar or Sugar Alcohol (%)	8±2%	9±2%	10±2%	11±2%	12±2%	13±2%	14±2%	15±2%
10-200	Var. 2041	Var. 2126	Var. 2211	Var. 2296	Var. 2381	Var. 2466	Var. 2551	Var. 2636
10-175	Var. 2042	Var. 2127	Var. 2212	Var. 2297	Var. 2382	Var. 2467	Var. 2552	Var. 2637
10-150	Var. 2043	Var. 2128	Var. 2213	Var. 2298	Var. 2383	Var. 2468	Var. 2553	Var. 2638
10-125	Var. 2044	Var. 2129	Var. 2214	Var. 2299	Var. 2384	Var. 2469	Var. 2554	Var. 2639
10-100	Var. 2045	Var. 2130	Var. 2215	Var. 2300	Var. 2385	Var. 2470	Var. 2555	Var. 2640
10-90	Var. 2046	Var. 2131	Var. 2216	Var. 2301	Var. 2386	Var. 2471	Var. 2556	Var. 2641
10-80	Var. 2047	Var. 2132	Var. 2217	Var. 2302	Var. 2387	Var. 2472	Var. 2557	Var. 2642
10-75	Var. 2048	Var. 2133	Var. 2218	Var. 2303	Var. 2388	Var. 2473	Var. 2558	Var. 2643
10-70	Var. 2049	Var. 2134	Var. 2219	Var. 2304	Var. 2389	Var. 2474	Var. 2559	Var. 2644
10-60	Var. 2050	Var. 2135	Var. 2220	Var. 2305	Var. 2390	Var. 2475	Var. 2560	Var. 2645
10-50	Var. 2051	Var. 2136	Var. 2221	Var. 2306	Var. 2391	Var. 2476	Var. 2561	Var. 2646
10-25	Var. 2052	Var. 2137	Var. 2222	Var. 2307	Var. 2392	Var. 2477	Var. 2562	Var. 2647
25-200	Var. 2053	Var. 2138	Var. 2223	Var. 2308	Var. 2393	Var. 2478	Var. 2563	Var. 2648
25-175	Var. 2054	Var. 2139	Var. 2224	Var. 2309	Var. 2394	Var. 2479	Var. 2564	Var. 2649
25-150	Var. 2055	Var. 2140	Var. 2225	Var. 2310	Var. 2395	Var. 2480	Var. 2565	Var. 2650
25-125	Var. 2056	Var. 2141	Var. 2226	Var. 2311	Var. 2396	Var. 2481	Var. 2566	Var. 2651
25-100	Var. 2057	Var. 2142	Var. 2227	Var. 2312	Var. 2397	Var. 2482	Var. 2567	Var. 2652
25-90	Var. 2058	Var. 2143	Var. 2228	Var. 2313	Var. 2398	Var. 2483	Var. 2568	Var. 2653
25-80	Var. 2059	Var. 2144	Var. 2229	Var. 2314	Var. 2399	Var. 2484	Var. 2569	Var. 2654
25-70	Var. 2060	Var. 2145	Var. 2230	Var. 2315	Var. 2400	Var. 2485	Var. 2570	Var. 2655
25-60	Var. 2061	Var. 2146	Var. 2231	Var. 2316	Var. 2401	Var. 2486	Var. 2571	Var. 2656
25-50	Var. 2062	Var. 2147	Var. 2232	Var. 2317	Var. 2402	Var. 2487	Var. 2572	Var. 2657
50-200	Var. 2063	Var. 2148	Var. 2233	Var. 2318	Var. 2403	Var. 2488	Var. 2573	Var. 2658
50-175	Var. 2064	Var. 2149	Var. 2234	Var. 2319	Var. 2404	Var. 2489	Var. 2574	Var. 2659
50-150	Var. 2065	Var. 2150	Var. 2235	Var. 2320	Var. 2405	Var. 2490	Var. 2575	Var. 2660
50-125	Var. 2066	Var. 2151	Var. 2236	Var. 2321	Var. 2406	Var. 2491	Var. 2576	Var. 2661
50-90	Var. 2067	Var. 2152	Var. 2237	Var. 2322	Var. 2407	Var. 2492	Var. 2577	Var. 2662
50-80	Var. 2068	Var. 2153	Var. 2238	Var. 2323	Var. 2408	Var. 2493	Var. 2578	Var. 2663
75-200	Var. 2069	Var. 2154	Var. 2239	Var. 2324	Var. 2409	Var. 2494	Var. 2579	Var. 2664
75-175	Var. 2070	Var. 2155	Var. 2240	Var. 2325	Var. 2410	Var. 2495	Var. 2580	Var. 2665
75-150	Var. 2071	Var. 2156	Var. 2241	Var. 2326	Var. 2411	Var. 2496	Var. 2581	Var. 2666
100-200	Var. 2072	Var. 2157	Var. 2242	Var. 2327	Var. 2412	Var. 2497	Var. 2582	Var. 2667
100-175	Var. 2073	Var. 2158	Var. 2243	Var. 2328	Var. 2413	Var. 2498	Var. 2583	Var. 2668
50±25	Var. 2074	Var. 2159	Var. 2244	Var. 2329	Var. 2414	Var. 2499	Var. 2584	Var. 2669
60±25	Var. 2075	Var. 2160	Var. 2245	Var. 2330	Var. 2415	Var. 2500	Var. 2585	Var. 2670
70±25	Var. 2076	Var. 2161	Var. 2246	Var. 2331	Var. 2416	Var. 2501	Var. 2586	Var. 2671
75±25	Var. 2077	Var. 2162	Var. 2247	Var. 2332	Var. 2417	Var. 2502	Var. 2587	Var. 2672
80±25	Var. 2078	Var. 2163	Var. 2248	Var. 2333	Var. 2418	Var. 2503	Var. 2588	Var. 2673

90±25	Var. 2079	Var. 2164	Var. 2249	Var. 2334	Var. 2419	Var. 2504	Var. 2589	Var. 2674
100±25	Var. 2080	Var. 2165	Var. 2250	Var. 2335	Var. 2420	Var. 2505	Var. 2590	Var. 2675
125±25	Var. 2081	Var. 2166	Var. 2251	Var. 2336	Var. 2421	Var. 2506	Var. 2591	Var. 2676
150±25	Var. 2082	Var. 2167	Var. 2252	Var. 2337	Var. 2422	Var. 2507	Var. 2592	Var. 2677
175±25	Var. 2083	Var. 2168	Var. 2253	Var. 2338	Var. 2423	Var. 2508	Var. 2593	Var. 2678
30±10	Var. 2084	Var. 2169	Var. 2254	Var. 2339	Var. 2424	Var. 2509	Var. 2594	Var. 2679
40±10	Var. 2085	Var. 2170	Var. 2255	Var. 2340	Var. 2425	Var. 2510	Var. 2595	Var. 2680
50±10	Var. 2086	Var. 2171	Var. 2256	Var. 2341	Var. 2426	Var. 2511	Var. 2596	Var. 2681
60±10	Var. 2087	Var. 2172	Var. 2257	Var. 2342	Var. 2427	Var. 2512	Var. 2597	Var. 2682
70±10	Var. 2088	Var. 2173	Var. 2258	Var. 2343	Var. 2428	Var. 2513	Var. 2598	Var. 2683
75±10	Var. 2089	Var. 2174	Var. 2259	Var. 2344	Var. 2429	Var. 2514	Var. 2599	Var. 2684
80±10	Var. 2090	Var. 2175	Var. 2260	Var. 2345	Var. 2430	Var. 2515	Var. 2600	Var. 2685
90±10	Var. 2091	Var. 2176	Var. 2261	Var. 2346	Var. 2431	Var. 2516	Var. 2601	Var. 2686
100±10	Var. 2092	Var. 2177	Var. 2262	Var. 2347	Var. 2432	Var. 2517	Var. 2602	Var. 2687
110±10	Var. 2093	Var. 2178	Var. 2263	Var. 2348	Var. 2433	Var. 2518	Var. 2603	Var. 2688
120±10	Var. 2094	Var. 2179	Var. 2264	Var. 2349	Var. 2434	Var. 2519	Var. 2604	Var. 2689
125±10	Var. 2095	Var. 2180	Var. 2265	Var. 2350	Var. 2435	Var. 2520	Var. 2605	Var. 2690
130±10	Var. 2096	Var. 2181	Var. 2266	Var. 2351	Var. 2436	Var. 2521	Var. 2606	Var. 2691
140±10	Var. 2097	Var. 2182	Var. 2267	Var. 2352	Var. 2437	Var. 2522	Var. 2607	Var. 2692
150±10	Var. 2098	Var. 2183	Var. 2268	Var. 2353	Var. 2438	Var. 2523	Var. 2608	Var. 2693
160±10	Var. 2099	Var. 2184	Var. 2269	Var. 2354	Var. 2439	Var. 2524	Var. 2609	Var. 2694
170±10	Var. 2100	Var. 2185	Var. 2270	Var. 2355	Var. 2440	Var. 2525	Var. 2610	Var. 2695
175±10	Var. 2101	Var. 2186	Var. 2271	Var. 2356	Var. 2441	Var. 2526	Var. 2611	Var. 2696
180±10	Var. 2102	Var. 2187	Var. 2272	Var. 2357	Var. 2442	Var. 2527	Var. 2612	Var. 2697
190±10	Var. 2103	Var. 2188	Var. 2273	Var. 2358	Var. 2443	Var. 2528	Var. 2613	Var. 2698
25	Var. 2104	Var. 2189	Var. 2274	Var. 2359	Var. 2444	Var. 2529	Var. 2614	Var. 2699
30	Var. 2105	Var. 2190	Var. 2275	Var. 2360	Var. 2445	Var. 2530	Var. 2615	Var. 2700
40	Var. 2106	Var. 2191	Var. 2276	Var. 2361	Var. 2446	Var. 2531	Var. 2616	Var. 2701
50	Var. 2107	Var. 2192	Var. 2277	Var. 2362	Var. 2447	Var. 2532	Var. 2617	Var. 2702
60	Var. 2108	Var. 2193	Var. 2278	Var. 2363	Var. 2448	Var. 2533	Var. 2618	Var. 2703
70	Var. 2109	Var. 2194	Var. 2279	Var. 2364	Var. 2449	Var. 2534	Var. 2619	Var. 2704
75	Var. 2110	Var. 2195	Var. 2280	Var. 2365	Var. 2450	Var. 2535	Var. 2620	Var. 2705
80	Var. 2111	Var. 2196	Var. 2281	Var. 2366	Var. 2451	Var. 2536	Var. 2621	Var. 2706
90	Var. 2112	Var. 2197	Var. 2282	Var. 2367	Var. 2452	Var. 2537	Var. 2622	Var. 2707
100	Var. 2113	Var. 2198	Var. 2283	Var. 2368	Var. 2453	Var. 2538	Var. 2623	Var. 2708
110	Var. 2114	Var. 2199	Var. 2284	Var. 2369	Var. 2454	Var. 2539	Var. 2624	Var. 2709
120	Var. 2115	Var. 2200	Var. 2285	Var. 2370	Var. 2455	Var. 2540	Var. 2625	Var. 2710
125	Var. 2116	Var. 2201	Var. 2286	Var. 2371	Var. 2456	Var. 2541	Var. 2626	Var. 2711
130	Var. 2117	Var. 2202	Var. 2287	Var. 2372	Var. 2457	Var. 2542	Var. 2627	Var. 2712
140	Var. 2118	Var. 2203	Var. 2288	Var. 2373	Var. 2458	Var. 2543	Var. 2628	Var. 2713
150	Var. 2119	Var. 2204	Var. 2289	Var. 2374	Var. 2459	Var. 2544	Var. 2629	Var. 2714
160	Var. 2120	Var. 2205	Var. 2290	Var. 2375	Var. 2460	Var. 2545	Var. 2630	Var. 2715
170	Var. 2121	Var. 2206	Var. 2291	Var. 2376	Var. 2461	Var. 2546	Var. 2631	Var. 2716

175	Var. 2122	Var. 2207	Var. 2292	Var. 2377	Var. 2462	Var. 2547	Var. 2632	Var. 2717
180	Var. 2123	Var. 2208	Var. 2293	Var. 2378	Var. 2463	Var. 2548	Var. 2633	Var. 2718
190	Var. 2124	Var. 2209	Var. 2294	Var. 2379	Var. 2464	Var. 2549	Var. 2634	Var. 2719
200	Var. 2125	Var. 2210	Var. 2295	Var. 2380	Var. 2465	Var. 2550	Var. 2635	Var. 2720

Var. = Variation

Table 5. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

	Sugar or Sugar Alcohol (%)							
Non-Ionic Surfactant (ppm)	16±2%	17±2%	18±2%	3±1%	4±1%	5±1%	6±1%	7±1%
10-200	Var. 2721	Var. 2806	Var. 2891	Var. 2976	Var. 3061	Var. 3146	Var. 3231	Var. 3316
10-175	Var. 2722	Var. 2807	Var. 2892	Var. 2977	Var. 3062	Var. 3147	Var. 3232	Var. 3317
10-150	Var. 2723	Var. 2808	Var. 2893	Var. 2978	Var. 3063	Var. 3148	Var. 3233	Var. 3318
10-125	Var. 2724	Var. 2809	Var. 2894	Var. 2979	Var. 3064	Var. 3149	Var. 3234	Var. 3319
10-100	Var. 2725	Var. 2810	Var. 2895	Var. 2980	Var. 3065	Var. 3150	Var. 3235	Var. 3320
10-90	Var. 2726	Var. 2811	Var. 2896	Var. 2981	Var. 3066	Var. 3151	Var. 3236	Var. 3321
10-80	Var. 2727	Var. 2812	Var. 2897	Var. 2982	Var. 3067	Var. 3152	Var. 3237	Var. 3322
10-75	Var. 2728	Var. 2813	Var. 2898	Var. 2983	Var. 3068	Var. 3153	Var. 3238	Var. 3323
10-70	Var. 2729	Var. 2814	Var. 2899	Var. 2984	Var. 3069	Var. 3154	Var. 3239	Var. 3324
10-60	Var. 2730	Var. 2815	Var. 2900	Var. 2985	Var. 3070	Var. 3155	Var. 3240	Var. 3325
10-50	Var. 2731	Var. 2816	Var. 2901	Var. 2986	Var. 3071	Var. 3156	Var. 3241	Var. 3326
10-25	Var. 2732	Var. 2817	Var. 2902	Var. 2987	Var. 3072	Var. 3157	Var. 3242	Var. 3327
25-200	Var. 2733	Var. 2818	Var. 2903	Var. 2988	Var. 3073	Var. 3158	Var. 3243	Var. 3328
25-175	Var. 2734	Var. 2819	Var. 2904	Var. 2989	Var. 3074	Var. 3159	Var. 3244	Var. 3329
25-150	Var. 2735	Var. 2820	Var. 2905	Var. 2990	Var. 3075	Var. 3160	Var. 3245	Var. 3330
25-125	Var. 2736	Var. 2821	Var. 2906	Var. 2991	Var. 3076	Var. 3161	Var. 3246	Var. 3331
25-100	Var. 2737	Var. 2822	Var. 2907	Var. 2992	Var. 3077	Var. 3162	Var. 3247	Var. 3332
25-90	Var. 2738	Var. 2823	Var. 2908	Var. 2993	Var. 3078	Var. 3163	Var. 3248	Var. 3333
25-80	Var. 2739	Var. 2824	Var. 2909	Var. 2994	Var. 3079	Var. 3164	Var. 3249	Var. 3334
25-70	Var. 2740	Var. 2825	Var. 2910	Var. 2995	Var. 3080	Var. 3165	Var. 3250	Var. 3335
25-60	Var. 2741	Var. 2826	Var. 2911	Var. 2996	Var. 3081	Var. 3166	Var. 3251	Var. 3336
25-50	Var. 2742	Var. 2827	Var. 2912	Var. 2997	Var. 3082	Var. 3167	Var. 3252	Var. 3337
50-200	Var. 2743	Var. 2828	Var. 2913	Var. 2998	Var. 3083	Var. 3168	Var. 3253	Var. 3338
50-175	Var. 2744	Var. 2829	Var. 2914	Var. 2999	Var. 3084	Var. 3169	Var. 3254	Var. 3339
50-150	Var. 2745	Var. 2830	Var. 2915	Var. 3000	Var. 3085	Var. 3170	Var. 3255	Var. 3340
50-125	Var. 2746	Var. 2831	Var. 2916	Var. 3001	Var. 3086	Var. 3171	Var. 3256	Var. 3341
50-90	Var. 2747	Var. 2832	Var. 2917	Var. 3002	Var. 3087	Var. 3172	Var. 3257	Var. 3342
50-80	Var. 2748	Var. 2833	Var. 2918	Var. 3003	Var. 3088	Var. 3173	Var. 3258	Var. 3343
75-200	Var. 2749	Var. 2834	Var. 2919	Var. 3004	Var. 3089	Var. 3174	Var. 3259	Var. 3344
75-175	Var. 2750	Var. 2835	Var. 2920	Var. 3005	Var. 3090	Var. 3175	Var. 3260	Var. 3345
75-150	Var. 2751	Var. 2836	Var. 2921	Var. 3006	Var. 3091	Var. 3176	Var. 3261	Var. 3346
100-200	Var. 2752	Var. 2837	Var. 2922	Var. 3007	Var. 3092	Var. 3177	Var. 3262	Var. 3347
100-175	Var. 2753	Var. 2838	Var. 2923	Var. 3008	Var. 3093	Var. 3178	Var. 3263	Var. 3348
50±25	Var. 2754	Var. 2839	Var. 2924	Var. 3009	Var. 3094	Var. 3179	Var. 3264	Var. 3349

60±25	Var. 2755	Var. 2840	Var. 2925	Var. 3010	Var. 3095	Var. 3180	Var. 3265	Var. 3350
70±25	Var. 2756	Var. 2841	Var. 2926	Var. 3011	Var. 3096	Var. 3181	Var. 3266	Var. 3351
75±25	Var. 2757	Var. 2842	Var. 2927	Var. 3012	Var. 3097	Var. 3182	Var. 3267	Var. 3352
80±25	Var. 2758	Var. 2843	Var. 2928	Var. 3013	Var. 3098	Var. 3183	Var. 3268	Var. 3353
90±25	Var. 2759	Var. 2844	Var. 2929	Var. 3014	Var. 3099	Var. 3184	Var. 3269	Var. 3354
100±25	Var. 2760	Var. 2845	Var. 2930	Var. 3015	Var. 3100	Var. 3185	Var. 3270	Var. 3355
125±25	Var. 2761	Var. 2846	Var. 2931	Var. 3016	Var. 3101	Var. 3186	Var. 3271	Var. 3356
150±25	Var. 2762	Var. 2847	Var. 2932	Var. 3017	Var. 3102	Var. 3187	Var. 3272	Var. 3357
175±25	Var. 2763	Var. 2848	Var. 2933	Var. 3018	Var. 3103	Var. 3188	Var. 3273	Var. 3358
30±10	Var. 2764	Var. 2849	Var. 2934	Var. 3019	Var. 3104	Var. 3189	Var. 3274	Var. 3359
40±10	Var. 2765	Var. 2850	Var. 2935	Var. 3020	Var. 3105	Var. 3190	Var. 3275	Var. 3360
50±10	Var. 2766	Var. 2851	Var. 2936	Var. 3021	Var. 3106	Var. 3191	Var. 3276	Var. 3361
60±10	Var. 2767	Var. 2852	Var. 2937	Var. 3022	Var. 3107	Var. 3192	Var. 3277	Var. 3362
70±10	Var. 2768	Var. 2853	Var. 2938	Var. 3023	Var. 3108	Var. 3193	Var. 3278	Var. 3363
75±10	Var. 2769	Var. 2854	Var. 2939	Var. 3024	Var. 3109	Var. 3194	Var. 3279	Var. 3364
80±10	Var. 2770	Var. 2855	Var. 2940	Var. 3025	Var. 3110	Var. 3195	Var. 3280	Var. 3365
90±10	Var. 2771	Var. 2856	Var. 2941	Var. 3026	Var. 3111	Var. 3196	Var. 3281	Var. 3366
100±10	Var. 2772	Var. 2857	Var. 2942	Var. 3027	Var. 3112	Var. 3197	Var. 3282	Var. 3367
110±10	Var. 2773	Var. 2858	Var. 2943	Var. 3028	Var. 3113	Var. 3198	Var. 3283	Var. 3368
120±10	Var. 2774	Var. 2859	Var. 2944	Var. 3029	Var. 3114	Var. 3199	Var. 3284	Var. 3369
125±10	Var. 2775	Var. 2860	Var. 2945	Var. 3030	Var. 3115	Var. 3200	Var. 3285	Var. 3370
130±10	Var. 2776	Var. 2861	Var. 2946	Var. 3031	Var. 3116	Var. 3201	Var. 3286	Var. 3371
140±10	Var. 2777	Var. 2862	Var. 2947	Var. 3032	Var. 3117	Var. 3202	Var. 3287	Var. 3372
150±10	Var. 2778	Var. 2863	Var. 2948	Var. 3033	Var. 3118	Var. 3203	Var. 3288	Var. 3373
160±10	Var. 2779	Var. 2864	Var. 2949	Var. 3034	Var. 3119	Var. 3204	Var. 3289	Var. 3374
170±10	Var. 2780	Var. 2865	Var. 2950	Var. 3035	Var. 3120	Var. 3205	Var. 3290	Var. 3375
175±10	Var. 2781	Var. 2866	Var. 2951	Var. 3036	Var. 3121	Var. 3206	Var. 3291	Var. 3376
180±10	Var. 2782	Var. 2867	Var. 2952	Var. 3037	Var. 3122	Var. 3207	Var. 3292	Var. 3377
190±10	Var. 2783	Var. 2868	Var. 2953	Var. 3038	Var. 3123	Var. 3208	Var. 3293	Var. 3378
25	Var. 2784	Var. 2869	Var. 2954	Var. 3039	Var. 3124	Var. 3209	Var. 3294	Var. 3379
30	Var. 2785	Var. 2870	Var. 2955	Var. 3040	Var. 3125	Var. 3210	Var. 3295	Var. 3380
40	Var. 2786	Var. 2871	Var. 2956	Var. 3041	Var. 3126	Var. 3211	Var. 3296	Var. 3381
50	Var. 2787	Var. 2872	Var. 2957	Var. 3042	Var. 3127	Var. 3212	Var. 3297	Var. 3382
60	Var. 2788	Var. 2873	Var. 2958	Var. 3043	Var. 3128	Var. 3213	Var. 3298	Var. 3383
70	Var. 2789	Var. 2874	Var. 2959	Var. 3044	Var. 3129	Var. 3214	Var. 3299	Var. 3384
75	Var. 2790	Var. 2875	Var. 2960	Var. 3045	Var. 3130	Var. 3215	Var. 3300	Var. 3385
80	Var. 2791	Var. 2876	Var. 2961	Var. 3046	Var. 3131	Var. 3216	Var. 3301	Var. 3386
90	Var. 2792	Var. 2877	Var. 2962	Var. 3047	Var. 3132	Var. 3217	Var. 3302	Var. 3387
100	Var. 2793	Var. 2878	Var. 2963	Var. 3048	Var. 3133	Var. 3218	Var. 3303	Var. 3388
110	Var. 2794	Var. 2879	Var. 2964	Var. 3049	Var. 3134	Var. 3219	Var. 3304	Var. 3389
120	Var. 2795	Var. 2880	Var. 2965	Var. 3050	Var. 3135	Var. 3220	Var. 3305	Var. 3390
125	Var. 2796	Var. 2881	Var. 2966	Var. 3051	Var. 3136	Var. 3221	Var. 3306	Var. 3391
130	Var. 2797	Var. 2882	Var. 2967	Var. 3052	Var. 3137	Var. 3222	Var. 3307	Var. 3392

140	Var. 2798	Var. 2883	Var. 2968	Var. 3053	Var. 3138	Var. 3223	Var. 3308	Var. 3393
150	Var. 2799	Var. 2884	Var. 2969	Var. 3054	Var. 3139	Var. 3224	Var. 3309	Var. 3394
160	Var. 2800	Var. 2885	Var. 2970	Var. 3055	Var. 3140	Var. 3225	Var. 3310	Var. 3395
170	Var. 2801	Var. 2886	Var. 2971	Var. 3056	Var. 3141	Var. 3226	Var. 3311	Var. 3396
175	Var. 2802	Var. 2887	Var. 2972	Var. 3057	Var. 3142	Var. 3227	Var. 3312	Var. 3397
180	Var. 2803	Var. 2888	Var. 2973	Var. 3058	Var. 3143	Var. 3228	Var. 3313	Var. 3398
190	Var. 2804	Var. 2889	Var. 2974	Var. 3059	Var. 3144	Var. 3229	Var. 3314	Var. 3399
200	Var. 2805	Var. 2890	Var. 2975	Var. 3060	Var. 3145	Var. 3230	Var. 3315	Var. 3400

Var. = Variation

Table 6. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

Non-Ionic Surfactant (ppm)	Sugar or Sugar Alcohol (%)							
	8±1%	9±1%	10±1%	11±1%	12±1%	13±1%	14±1%	15±1%
10-200	Var. 3401	Var. 3486	Var. 3571	Var. 3656	Var. 3741	Var. 3826	Var. 3911	Var. 3996
10-175	Var. 3402	Var. 3487	Var. 3572	Var. 3657	Var. 3742	Var. 3827	Var. 3912	Var. 3997
10-150	Var. 3403	Var. 3488	Var. 3573	Var. 3658	Var. 3743	Var. 3828	Var. 3913	Var. 3998
10-125	Var. 3404	Var. 3489	Var. 3574	Var. 3659	Var. 3744	Var. 3829	Var. 3914	Var. 3999
10-100	Var. 3405	Var. 3490	Var. 3575	Var. 3660	Var. 3745	Var. 3830	Var. 3915	Var. 4000
10-90	Var. 3406	Var. 3491	Var. 3576	Var. 3661	Var. 3746	Var. 3831	Var. 3916	Var. 4001
10-80	Var. 3407	Var. 3492	Var. 3577	Var. 3662	Var. 3747	Var. 3832	Var. 3917	Var. 4002
10-75	Var. 3408	Var. 3493	Var. 3578	Var. 3663	Var. 3748	Var. 3833	Var. 3918	Var. 4003
10-70	Var. 3409	Var. 3494	Var. 3579	Var. 3664	Var. 3749	Var. 3834	Var. 3919	Var. 4004
10-60	Var. 3410	Var. 3495	Var. 3580	Var. 3665	Var. 3750	Var. 3835	Var. 3920	Var. 4005
10-50	Var. 3411	Var. 3496	Var. 3581	Var. 3666	Var. 3751	Var. 3836	Var. 3921	Var. 4006
10-25	Var. 3412	Var. 3497	Var. 3582	Var. 3667	Var. 3752	Var. 3837	Var. 3922	Var. 4007
25-200	Var. 3413	Var. 3498	Var. 3583	Var. 3668	Var. 3753	Var. 3838	Var. 3923	Var. 4008
25-175	Var. 3414	Var. 3499	Var. 3584	Var. 3669	Var. 3754	Var. 3839	Var. 3924	Var. 4009
25-150	Var. 3415	Var. 3500	Var. 3585	Var. 3670	Var. 3755	Var. 3840	Var. 3925	Var. 4010
25-125	Var. 3416	Var. 3501	Var. 3586	Var. 3671	Var. 3756	Var. 3841	Var. 3926	Var. 4011
25-100	Var. 3417	Var. 3502	Var. 3587	Var. 3672	Var. 3757	Var. 3842	Var. 3927	Var. 4012
25-90	Var. 3418	Var. 3503	Var. 3588	Var. 3673	Var. 3758	Var. 3843	Var. 3928	Var. 4013
25-80	Var. 3419	Var. 3504	Var. 3589	Var. 3674	Var. 3759	Var. 3844	Var. 3929	Var. 4014
25-70	Var. 3420	Var. 3505	Var. 3590	Var. 3675	Var. 3760	Var. 3845	Var. 3930	Var. 4015
25-60	Var. 3421	Var. 3506	Var. 3591	Var. 3676	Var. 3761	Var. 3846	Var. 3931	Var. 4016
25-50	Var. 3422	Var. 3507	Var. 3592	Var. 3677	Var. 3762	Var. 3847	Var. 3932	Var. 4017
50-200	Var. 3423	Var. 3508	Var. 3593	Var. 3678	Var. 3763	Var. 3848	Var. 3933	Var. 4018
50-175	Var. 3424	Var. 3509	Var. 3594	Var. 3679	Var. 3764	Var. 3849	Var. 3934	Var. 4019
50-150	Var. 3425	Var. 3510	Var. 3595	Var. 3680	Var. 3765	Var. 3850	Var. 3935	Var. 4020
50-125	Var. 3426	Var. 3511	Var. 3596	Var. 3681	Var. 3766	Var. 3851	Var. 3936	Var. 4021
50-90	Var. 3427	Var. 3512	Var. 3597	Var. 3682	Var. 3767	Var. 3852	Var. 3937	Var. 4022
50-80	Var. 3428	Var. 3513	Var. 3598	Var. 3683	Var. 3768	Var. 3853	Var. 3938	Var. 4023
75-200	Var. 3429	Var. 3514	Var. 3599	Var. 3684	Var. 3769	Var. 3854	Var. 3939	Var. 4024
75-175	Var. 3430	Var. 3515	Var. 3600	Var. 3685	Var. 3770	Var. 3855	Var. 3940	Var. 4025

75-150	Var. 3431	Var. 3516	Var. 3601	Var. 3686	Var. 3771	Var. 3856	Var. 3941	Var. 4026
100-200	Var. 3432	Var. 3517	Var. 3602	Var. 3687	Var. 3772	Var. 3857	Var. 3942	Var. 4027
100-175	Var. 3433	Var. 3518	Var. 3603	Var. 3688	Var. 3773	Var. 3858	Var. 3943	Var. 4028
50±25	Var. 3434	Var. 3519	Var. 3604	Var. 3689	Var. 3774	Var. 3859	Var. 3944	Var. 4029
60±25	Var. 3435	Var. 3520	Var. 3605	Var. 3690	Var. 3775	Var. 3860	Var. 3945	Var. 4030
70±25	Var. 3436	Var. 3521	Var. 3606	Var. 3691	Var. 3776	Var. 3861	Var. 3946	Var. 4031
75±25	Var. 3437	Var. 3522	Var. 3607	Var. 3692	Var. 3777	Var. 3862	Var. 3947	Var. 4032
80±25	Var. 3438	Var. 3523	Var. 3608	Var. 3693	Var. 3778	Var. 3863	Var. 3948	Var. 4033
90±25	Var. 3439	Var. 3524	Var. 3609	Var. 3694	Var. 3779	Var. 3864	Var. 3949	Var. 4034
100±25	Var. 3440	Var. 3525	Var. 3610	Var. 3695	Var. 3780	Var. 3865	Var. 3950	Var. 4035
125±25	Var. 3441	Var. 3526	Var. 3611	Var. 3696	Var. 3781	Var. 3866	Var. 3951	Var. 4036
150±25	Var. 3442	Var. 3527	Var. 3612	Var. 3697	Var. 3782	Var. 3867	Var. 3952	Var. 4037
175±25	Var. 3443	Var. 3528	Var. 3613	Var. 3698	Var. 3783	Var. 3868	Var. 3953	Var. 4038
30±10	Var. 3444	Var. 3529	Var. 3614	Var. 3699	Var. 3784	Var. 3869	Var. 3954	Var. 4039
40±10	Var. 3445	Var. 3530	Var. 3615	Var. 3700	Var. 3785	Var. 3870	Var. 3955	Var. 4040
50±10	Var. 3446	Var. 3531	Var. 3616	Var. 3701	Var. 3786	Var. 3871	Var. 3956	Var. 4041
60±10	Var. 3447	Var. 3532	Var. 3617	Var. 3702	Var. 3787	Var. 3872	Var. 3957	Var. 4042
70±10	Var. 3448	Var. 3533	Var. 3618	Var. 3703	Var. 3788	Var. 3873	Var. 3958	Var. 4043
75±10	Var. 3449	Var. 3534	Var. 3619	Var. 3704	Var. 3789	Var. 3874	Var. 3959	Var. 4044
80±10	Var. 3450	Var. 3535	Var. 3620	Var. 3705	Var. 3790	Var. 3875	Var. 3960	Var. 4045
90±10	Var. 3451	Var. 3536	Var. 3621	Var. 3706	Var. 3791	Var. 3876	Var. 3961	Var. 4046
100±10	Var. 3452	Var. 3537	Var. 3622	Var. 3707	Var. 3792	Var. 3877	Var. 3962	Var. 4047
110±10	Var. 3453	Var. 3538	Var. 3623	Var. 3708	Var. 3793	Var. 3878	Var. 3963	Var. 4048
120±10	Var. 3454	Var. 3539	Var. 3624	Var. 3709	Var. 3794	Var. 3879	Var. 3964	Var. 4049
125±10	Var. 3455	Var. 3540	Var. 3625	Var. 3710	Var. 3795	Var. 3880	Var. 3965	Var. 4050
130±10	Var. 3456	Var. 3541	Var. 3626	Var. 3711	Var. 3796	Var. 3881	Var. 3966	Var. 4051
140±10	Var. 3457	Var. 3542	Var. 3627	Var. 3712	Var. 3797	Var. 3882	Var. 3967	Var. 4052
150±10	Var. 3458	Var. 3543	Var. 3628	Var. 3713	Var. 3798	Var. 3883	Var. 3968	Var. 4053
160±10	Var. 3459	Var. 3544	Var. 3629	Var. 3714	Var. 3799	Var. 3884	Var. 3969	Var. 4054
170±10	Var. 3460	Var. 3545	Var. 3630	Var. 3715	Var. 3800	Var. 3885	Var. 3970	Var. 4055
175±10	Var. 3461	Var. 3546	Var. 3631	Var. 3716	Var. 3801	Var. 3886	Var. 3971	Var. 4056
180±10	Var. 3462	Var. 3547	Var. 3632	Var. 3717	Var. 3802	Var. 3887	Var. 3972	Var. 4057
190±10	Var. 3463	Var. 3548	Var. 3633	Var. 3718	Var. 3803	Var. 3888	Var. 3973	Var. 4058
25	Var. 3464	Var. 3549	Var. 3634	Var. 3719	Var. 3804	Var. 3889	Var. 3974	Var. 4059
30	Var. 3465	Var. 3550	Var. 3635	Var. 3720	Var. 3805	Var. 3890	Var. 3975	Var. 4060
40	Var. 3466	Var. 3551	Var. 3636	Var. 3721	Var. 3806	Var. 3891	Var. 3976	Var. 4061
50	Var. 3467	Var. 3552	Var. 3637	Var. 3722	Var. 3807	Var. 3892	Var. 3977	Var. 4062
60	Var. 3468	Var. 3553	Var. 3638	Var. 3723	Var. 3808	Var. 3893	Var. 3978	Var. 4063
70	Var. 3469	Var. 3554	Var. 3639	Var. 3724	Var. 3809	Var. 3894	Var. 3979	Var. 4064
75	Var. 3470	Var. 3555	Var. 3640	Var. 3725	Var. 3810	Var. 3895	Var. 3980	Var. 4065
80	Var. 3471	Var. 3556	Var. 3641	Var. 3726	Var. 3811	Var. 3896	Var. 3981	Var. 4066
90	Var. 3472	Var. 3557	Var. 3642	Var. 3727	Var. 3812	Var. 3897	Var. 3982	Var. 4067
100	Var. 3473	Var. 3558	Var. 3643	Var. 3728	Var. 3813	Var. 3898	Var. 3983	Var. 4068

110	Var. 3474	Var. 3559	Var. 3644	Var. 3729	Var. 3814	Var. 3899	Var. 3984	Var. 4069
120	Var. 3475	Var. 3560	Var. 3645	Var. 3730	Var. 3815	Var. 3900	Var. 3985	Var. 4070
125	Var. 3476	Var. 3561	Var. 3646	Var. 3731	Var. 3816	Var. 3901	Var. 3986	Var. 4071
130	Var. 3477	Var. 3562	Var. 3647	Var. 3732	Var. 3817	Var. 3902	Var. 3987	Var. 4072
140	Var. 3478	Var. 3563	Var. 3648	Var. 3733	Var. 3818	Var. 3903	Var. 3988	Var. 4073
150	Var. 3479	Var. 3564	Var. 3649	Var. 3734	Var. 3819	Var. 3904	Var. 3989	Var. 4074
160	Var. 3480	Var. 3565	Var. 3650	Var. 3735	Var. 3820	Var. 3905	Var. 3990	Var. 4075
170	Var. 3481	Var. 3566	Var. 3651	Var. 3736	Var. 3821	Var. 3906	Var. 3991	Var. 4076
175	Var. 3482	Var. 3567	Var. 3652	Var. 3737	Var. 3822	Var. 3907	Var. 3992	Var. 4077
180	Var. 3483	Var. 3568	Var. 3653	Var. 3738	Var. 3823	Var. 3908	Var. 3993	Var. 4078
190	Var. 3484	Var. 3569	Var. 3654	Var. 3739	Var. 3824	Var. 3909	Var. 3994	Var. 4079
200	Var. 3485	Var. 3570	Var. 3655	Var. 3740	Var. 3825	Var. 3910	Var. 3995	Var. 4080

Var. = Variation

Table 7. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

Non-Ionic Surfactant (ppm)	Sugar or Sugar Alcohol (%)							
	16±1%	17±1%	18±1%	19±1%	2%	3%	4%	5%
10-200	Var. 4081	Var. 4166	Var. 4251	Var. 4336	Var. 4421	Var. 4506	Var. 4591	Var. 4676
10-175	Var. 4082	Var. 4167	Var. 4252	Var. 4337	Var. 4422	Var. 4507	Var. 4592	Var. 4677
10-150	Var. 4083	Var. 4168	Var. 4253	Var. 4338	Var. 4423	Var. 4508	Var. 4593	Var. 4678
10-125	Var. 4084	Var. 4169	Var. 4254	Var. 4339	Var. 4424	Var. 4509	Var. 4594	Var. 4679
10-100	Var. 4085	Var. 4170	Var. 4255	Var. 4340	Var. 4425	Var. 4510	Var. 4595	Var. 4680
10-90	Var. 4086	Var. 4171	Var. 4256	Var. 4341	Var. 4426	Var. 4511	Var. 4596	Var. 4681
10-80	Var. 4087	Var. 4172	Var. 4257	Var. 4342	Var. 4427	Var. 4512	Var. 4597	Var. 4682
10-75	Var. 4088	Var. 4173	Var. 4258	Var. 4343	Var. 4428	Var. 4513	Var. 4598	Var. 4683
10-70	Var. 4089	Var. 4174	Var. 4259	Var. 4344	Var. 4429	Var. 4514	Var. 4599	Var. 4684
10-60	Var. 4090	Var. 4175	Var. 4260	Var. 4345	Var. 4430	Var. 4515	Var. 4600	Var. 4685
10-50	Var. 4091	Var. 4176	Var. 4261	Var. 4346	Var. 4431	Var. 4516	Var. 4601	Var. 4686
10-25	Var. 4092	Var. 4177	Var. 4262	Var. 4347	Var. 4432	Var. 4517	Var. 4602	Var. 4687
25-200	Var. 4093	Var. 4178	Var. 4263	Var. 4348	Var. 4433	Var. 4518	Var. 4603	Var. 4688
25-175	Var. 4094	Var. 4179	Var. 4264	Var. 4349	Var. 4434	Var. 4519	Var. 4604	Var. 4689
25-150	Var. 4095	Var. 4180	Var. 4265	Var. 4350	Var. 4435	Var. 4520	Var. 4605	Var. 4690
25-125	Var. 4096	Var. 4181	Var. 4266	Var. 4351	Var. 4436	Var. 4521	Var. 4606	Var. 4691
25-100	Var. 4097	Var. 4182	Var. 4267	Var. 4352	Var. 4437	Var. 4522	Var. 4607	Var. 4692
25-90	Var. 4098	Var. 4183	Var. 4268	Var. 4353	Var. 4438	Var. 4523	Var. 4608	Var. 4693
25-80	Var. 4099	Var. 4184	Var. 4269	Var. 4354	Var. 4439	Var. 4524	Var. 4609	Var. 4694
25-70	Var. 4100	Var. 4185	Var. 4270	Var. 4355	Var. 4440	Var. 4525	Var. 4610	Var. 4695
25-60	Var. 4101	Var. 4186	Var. 4271	Var. 4356	Var. 4441	Var. 4526	Var. 4611	Var. 4696
25-50	Var. 4102	Var. 4187	Var. 4272	Var. 4357	Var. 4442	Var. 4527	Var. 4612	Var. 4697
50-200	Var. 4103	Var. 4188	Var. 4273	Var. 4358	Var. 4443	Var. 4528	Var. 4613	Var. 4698
50-175	Var. 4104	Var. 4189	Var. 4274	Var. 4359	Var. 4444	Var. 4529	Var. 4614	Var. 4699
50-150	Var. 4105	Var. 4190	Var. 4275	Var. 4360	Var. 4445	Var. 4530	Var. 4615	Var. 4700
50-125	Var. 4106	Var. 4191	Var. 4276	Var. 4361	Var. 4446	Var. 4531	Var. 4616	Var. 4701

50-90	Var. 4107	Var. 4192	Var. 4277	Var. 4362	Var. 4447	Var. 4532	Var. 4617	Var. 4702
50-80	Var. 4108	Var. 4193	Var. 4278	Var. 4363	Var. 4448	Var. 4533	Var. 4618	Var. 4703
75-200	Var. 4109	Var. 4194	Var. 4279	Var. 4364	Var. 4449	Var. 4534	Var. 4619	Var. 4704
75-175	Var. 4110	Var. 4195	Var. 4280	Var. 4365	Var. 4450	Var. 4535	Var. 4620	Var. 4705
75-150	Var. 4111	Var. 4196	Var. 4281	Var. 4366	Var. 4451	Var. 4536	Var. 4621	Var. 4706
100-200	Var. 4112	Var. 4197	Var. 4282	Var. 4367	Var. 4452	Var. 4537	Var. 4622	Var. 4707
100-175	Var. 4113	Var. 4198	Var. 4283	Var. 4368	Var. 4453	Var. 4538	Var. 4623	Var. 4708
50±25	Var. 4114	Var. 4199	Var. 4284	Var. 4369	Var. 4454	Var. 4539	Var. 4624	Var. 4709
60±25	Var. 4115	Var. 4200	Var. 4285	Var. 4370	Var. 4455	Var. 4540	Var. 4625	Var. 4710
70±25	Var. 4116	Var. 4201	Var. 4286	Var. 4371	Var. 4456	Var. 4541	Var. 4626	Var. 4711
75±25	Var. 4117	Var. 4202	Var. 4287	Var. 4372	Var. 4457	Var. 4542	Var. 4627	Var. 4712
80±25	Var. 4118	Var. 4203	Var. 4288	Var. 4373	Var. 4458	Var. 4543	Var. 4628	Var. 4713
90±25	Var. 4119	Var. 4204	Var. 4289	Var. 4374	Var. 4459	Var. 4544	Var. 4629	Var. 4714
100±25	Var. 4120	Var. 4205	Var. 4290	Var. 4375	Var. 4460	Var. 4545	Var. 4630	Var. 4715
125±25	Var. 4121	Var. 4206	Var. 4291	Var. 4376	Var. 4461	Var. 4546	Var. 4631	Var. 4716
150±25	Var. 4122	Var. 4207	Var. 4292	Var. 4377	Var. 4462	Var. 4547	Var. 4632	Var. 4717
175±25	Var. 4123	Var. 4208	Var. 4293	Var. 4378	Var. 4463	Var. 4548	Var. 4633	Var. 4718
30±10	Var. 4124	Var. 4209	Var. 4294	Var. 4379	Var. 4464	Var. 4549	Var. 4634	Var. 4719
40±10	Var. 4125	Var. 4210	Var. 4295	Var. 4380	Var. 4465	Var. 4550	Var. 4635	Var. 4720
50±10	Var. 4126	Var. 4211	Var. 4296	Var. 4381	Var. 4466	Var. 4551	Var. 4636	Var. 4721
60±10	Var. 4127	Var. 4212	Var. 4297	Var. 4382	Var. 4467	Var. 4552	Var. 4637	Var. 4722
70±10	Var. 4128	Var. 4213	Var. 4298	Var. 4383	Var. 4468	Var. 4553	Var. 4638	Var. 4723
75±10	Var. 4129	Var. 4214	Var. 4299	Var. 4384	Var. 4469	Var. 4554	Var. 4639	Var. 4724
80±10	Var. 4130	Var. 4215	Var. 4300	Var. 4385	Var. 4470	Var. 4555	Var. 4640	Var. 4725
90±10	Var. 4131	Var. 4216	Var. 4301	Var. 4386	Var. 4471	Var. 4556	Var. 4641	Var. 4726
100±10	Var. 4132	Var. 4217	Var. 4302	Var. 4387	Var. 4472	Var. 4557	Var. 4642	Var. 4727
110±10	Var. 4133	Var. 4218	Var. 4303	Var. 4388	Var. 4473	Var. 4558	Var. 4643	Var. 4728
120±10	Var. 4134	Var. 4219	Var. 4304	Var. 4389	Var. 4474	Var. 4559	Var. 4644	Var. 4729
125±10	Var. 4135	Var. 4220	Var. 4305	Var. 4390	Var. 4475	Var. 4560	Var. 4645	Var. 4730
130±10	Var. 4136	Var. 4221	Var. 4306	Var. 4391	Var. 4476	Var. 4561	Var. 4646	Var. 4731
140±10	Var. 4137	Var. 4222	Var. 4307	Var. 4392	Var. 4477	Var. 4562	Var. 4647	Var. 4732
150±10	Var. 4138	Var. 4223	Var. 4308	Var. 4393	Var. 4478	Var. 4563	Var. 4648	Var. 4733
160±10	Var. 4139	Var. 4224	Var. 4309	Var. 4394	Var. 4479	Var. 4564	Var. 4649	Var. 4734
170±10	Var. 4140	Var. 4225	Var. 4310	Var. 4395	Var. 4480	Var. 4565	Var. 4650	Var. 4735
175±10	Var. 4141	Var. 4226	Var. 4311	Var. 4396	Var. 4481	Var. 4566	Var. 4651	Var. 4736
180±10	Var. 4142	Var. 4227	Var. 4312	Var. 4397	Var. 4482	Var. 4567	Var. 4652	Var. 4737
190±10	Var. 4143	Var. 4228	Var. 4313	Var. 4398	Var. 4483	Var. 4568	Var. 4653	Var. 4738
25	Var. 4144	Var. 4229	Var. 4314	Var. 4399	Var. 4484	Var. 4569	Var. 4654	Var. 4739
30	Var. 4145	Var. 4230	Var. 4315	Var. 4400	Var. 4485	Var. 4570	Var. 4655	Var. 4740
40	Var. 4146	Var. 4231	Var. 4316	Var. 4401	Var. 4486	Var. 4571	Var. 4656	Var. 4741
50	Var. 4147	Var. 4232	Var. 4317	Var. 4402	Var. 4487	Var. 4572	Var. 4657	Var. 4742
60	Var. 4148	Var. 4233	Var. 4318	Var. 4403	Var. 4488	Var. 4573	Var. 4658	Var. 4743
70	Var. 4149	Var. 4234	Var. 4319	Var. 4404	Var. 4489	Var. 4574	Var. 4659	Var. 4744

75	Var. 4150	Var. 4235	Var. 4320	Var. 4405	Var. 4490	Var. 4575	Var. 4660	Var. 4745
80	Var. 4151	Var. 4236	Var. 4321	Var. 4406	Var. 4491	Var. 4576	Var. 4661	Var. 4746
90	Var. 4152	Var. 4237	Var. 4322	Var. 4407	Var. 4492	Var. 4577	Var. 4662	Var. 4747
100	Var. 4153	Var. 4238	Var. 4323	Var. 4408	Var. 4493	Var. 4578	Var. 4663	Var. 4748
110	Var. 4154	Var. 4239	Var. 4324	Var. 4409	Var. 4494	Var. 4579	Var. 4664	Var. 4749
120	Var. 4155	Var. 4240	Var. 4325	Var. 4410	Var. 4495	Var. 4580	Var. 4665	Var. 4750
125	Var. 4156	Var. 4241	Var. 4326	Var. 4411	Var. 4496	Var. 4581	Var. 4666	Var. 4751
130	Var. 4157	Var. 4242	Var. 4327	Var. 4412	Var. 4497	Var. 4582	Var. 4667	Var. 4752
140	Var. 4158	Var. 4243	Var. 4328	Var. 4413	Var. 4498	Var. 4583	Var. 4668	Var. 4753
150	Var. 4159	Var. 4244	Var. 4329	Var. 4414	Var. 4499	Var. 4584	Var. 4669	Var. 4754
160	Var. 4160	Var. 4245	Var. 4330	Var. 4415	Var. 4500	Var. 4585	Var. 4670	Var. 4755
170	Var. 4161	Var. 4246	Var. 4331	Var. 4416	Var. 4501	Var. 4586	Var. 4671	Var. 4756
175	Var. 4162	Var. 4247	Var. 4332	Var. 4417	Var. 4502	Var. 4587	Var. 4672	Var. 4757
180	Var. 4163	Var. 4248	Var. 4333	Var. 4418	Var. 4503	Var. 4588	Var. 4673	Var. 4758
190	Var. 4164	Var. 4249	Var. 4334	Var. 4419	Var. 4504	Var. 4589	Var. 4674	Var. 4759
200	Var. 4165	Var. 4250	Var. 4335	Var. 4420	Var. 4505	Var. 4590	Var. 4675	Var. 4760

Var. = Variation

Table 8. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

	Sugar or Sugar Alcohol (%)							
Non-Ionic Surfactant (ppm)	6%	7%	8%	9%	10%	11%	12%	13%
10-200	Var. 4761	Var. 4846	Var. 4931	Var. 5016	Var. 5101	Var. 5186	Var. 5271	Var. 5356
10-175	Var. 4762	Var. 4847	Var. 4932	Var. 5017	Var. 5102	Var. 5187	Var. 5272	Var. 5357
10-150	Var. 4763	Var. 4848	Var. 4933	Var. 5018	Var. 5103	Var. 5188	Var. 5273	Var. 5358
10-125	Var. 4764	Var. 4849	Var. 4934	Var. 5019	Var. 5104	Var. 5189	Var. 5274	Var. 5359
10-100	Var. 4765	Var. 4850	Var. 4935	Var. 5020	Var. 5105	Var. 5190	Var. 5275	Var. 5360
10-90	Var. 4766	Var. 4851	Var. 4936	Var. 5021	Var. 5106	Var. 5191	Var. 5276	Var. 5361
10-80	Var. 4767	Var. 4852	Var. 4937	Var. 5022	Var. 5107	Var. 5192	Var. 5277	Var. 5362
10-75	Var. 4768	Var. 4853	Var. 4938	Var. 5023	Var. 5108	Var. 5193	Var. 5278	Var. 5363
10-70	Var. 4769	Var. 4854	Var. 4939	Var. 5024	Var. 5109	Var. 5194	Var. 5279	Var. 5364
10-60	Var. 4770	Var. 4855	Var. 4940	Var. 5025	Var. 5110	Var. 5195	Var. 5280	Var. 5365
10-50	Var. 4771	Var. 4856	Var. 4941	Var. 5026	Var. 5111	Var. 5196	Var. 5281	Var. 5366
10-25	Var. 4772	Var. 4857	Var. 4942	Var. 5027	Var. 5112	Var. 5197	Var. 5282	Var. 5367
25-200	Var. 4773	Var. 4858	Var. 4943	Var. 5028	Var. 5113	Var. 5198	Var. 5283	Var. 5368
25-175	Var. 4774	Var. 4859	Var. 4944	Var. 5029	Var. 5114	Var. 5199	Var. 5284	Var. 5369
25-150	Var. 4775	Var. 4860	Var. 4945	Var. 5030	Var. 5115	Var. 5200	Var. 5285	Var. 5370
25-125	Var. 4776	Var. 4861	Var. 4946	Var. 5031	Var. 5116	Var. 5201	Var. 5286	Var. 5371
25-100	Var. 4777	Var. 4862	Var. 4947	Var. 5032	Var. 5117	Var. 5202	Var. 5287	Var. 5372
25-90	Var. 4778	Var. 4863	Var. 4948	Var. 5033	Var. 5118	Var. 5203	Var. 5288	Var. 5373
25-80	Var. 4779	Var. 4864	Var. 4949	Var. 5034	Var. 5119	Var. 5204	Var. 5289	Var. 5374
25-70	Var. 4780	Var. 4865	Var. 4950	Var. 5035	Var. 5120	Var. 5205	Var. 5290	Var. 5375
25-60	Var. 4781	Var. 4866	Var. 4951	Var. 5036	Var. 5121	Var. 5206	Var. 5291	Var. 5376
25-50	Var. 4782	Var. 4867	Var. 4952	Var. 5037	Var. 5122	Var. 5207	Var. 5292	Var. 5377

50-200	Var. 4783	Var. 4868	Var. 4953	Var. 5038	Var. 5123	Var. 5208	Var. 5293	Var. 5378
50-175	Var. 4784	Var. 4869	Var. 4954	Var. 5039	Var. 5124	Var. 5209	Var. 5294	Var. 5379
50-150	Var. 4785	Var. 4870	Var. 4955	Var. 5040	Var. 5125	Var. 5210	Var. 5295	Var. 5380
50-125	Var. 4786	Var. 4871	Var. 4956	Var. 5041	Var. 5126	Var. 5211	Var. 5296	Var. 5381
50-90	Var. 4787	Var. 4872	Var. 4957	Var. 5042	Var. 5127	Var. 5212	Var. 5297	Var. 5382
50-80	Var. 4788	Var. 4873	Var. 4958	Var. 5043	Var. 5128	Var. 5213	Var. 5298	Var. 5383
75-200	Var. 4789	Var. 4874	Var. 4959	Var. 5044	Var. 5129	Var. 5214	Var. 5299	Var. 5384
75-175	Var. 4790	Var. 4875	Var. 4960	Var. 5045	Var. 5130	Var. 5215	Var. 5300	Var. 5385
75-150	Var. 4791	Var. 4876	Var. 4961	Var. 5046	Var. 5131	Var. 5216	Var. 5301	Var. 5386
100-200	Var. 4792	Var. 4877	Var. 4962	Var. 5047	Var. 5132	Var. 5217	Var. 5302	Var. 5387
100-175	Var. 4793	Var. 4878	Var. 4963	Var. 5048	Var. 5133	Var. 5218	Var. 5303	Var. 5388
50±25	Var. 4794	Var. 4879	Var. 4964	Var. 5049	Var. 5134	Var. 5219	Var. 5304	Var. 5389
60±25	Var. 4795	Var. 4880	Var. 4965	Var. 5050	Var. 5135	Var. 5220	Var. 5305	Var. 5390
70±25	Var. 4796	Var. 4881	Var. 4966	Var. 5051	Var. 5136	Var. 5221	Var. 5306	Var. 5391
75±25	Var. 4797	Var. 4882	Var. 4967	Var. 5052	Var. 5137	Var. 5222	Var. 5307	Var. 5392
80±25	Var. 4798	Var. 4883	Var. 4968	Var. 5053	Var. 5138	Var. 5223	Var. 5308	Var. 5393
90±25	Var. 4799	Var. 4884	Var. 4969	Var. 5054	Var. 5139	Var. 5224	Var. 5309	Var. 5394
100±25	Var. 4800	Var. 4885	Var. 4970	Var. 5055	Var. 5140	Var. 5225	Var. 5310	Var. 5395
125±25	Var. 4801	Var. 4886	Var. 4971	Var. 5056	Var. 5141	Var. 5226	Var. 5311	Var. 5396
150±25	Var. 4802	Var. 4887	Var. 4972	Var. 5057	Var. 5142	Var. 5227	Var. 5312	Var. 5397
175±25	Var. 4803	Var. 4888	Var. 4973	Var. 5058	Var. 5143	Var. 5228	Var. 5313	Var. 5398
30±10	Var. 4804	Var. 4889	Var. 4974	Var. 5059	Var. 5144	Var. 5229	Var. 5314	Var. 5399
40±10	Var. 4805	Var. 4890	Var. 4975	Var. 5060	Var. 5145	Var. 5230	Var. 5315	Var. 5400
50±10	Var. 4806	Var. 4891	Var. 4976	Var. 5061	Var. 5146	Var. 5231	Var. 5316	Var. 5401
60±10	Var. 4807	Var. 4892	Var. 4977	Var. 5062	Var. 5147	Var. 5232	Var. 5317	Var. 5402
70±10	Var. 4808	Var. 4893	Var. 4978	Var. 5063	Var. 5148	Var. 5233	Var. 5318	Var. 5403
75±10	Var. 4809	Var. 4894	Var. 4979	Var. 5064	Var. 5149	Var. 5234	Var. 5319	Var. 5404
80±10	Var. 4810	Var. 4895	Var. 4980	Var. 5065	Var. 5150	Var. 5235	Var. 5320	Var. 5405
90±10	Var. 4811	Var. 4896	Var. 4981	Var. 5066	Var. 5151	Var. 5236	Var. 5321	Var. 5406
100±10	Var. 4812	Var. 4897	Var. 4982	Var. 5067	Var. 5152	Var. 5237	Var. 5322	Var. 5407
110±10	Var. 4813	Var. 4898	Var. 4983	Var. 5068	Var. 5153	Var. 5238	Var. 5323	Var. 5408
120±10	Var. 4814	Var. 4899	Var. 4984	Var. 5069	Var. 5154	Var. 5239	Var. 5324	Var. 5409
125±10	Var. 4815	Var. 4900	Var. 4985	Var. 5070	Var. 5155	Var. 5240	Var. 5325	Var. 5410
130±10	Var. 4816	Var. 4901	Var. 4986	Var. 5071	Var. 5156	Var. 5241	Var. 5326	Var. 5411
140±10	Var. 4817	Var. 4902	Var. 4987	Var. 5072	Var. 5157	Var. 5242	Var. 5327	Var. 5412
150±10	Var. 4818	Var. 4903	Var. 4988	Var. 5073	Var. 5158	Var. 5243	Var. 5328	Var. 5413
160±10	Var. 4819	Var. 4904	Var. 4989	Var. 5074	Var. 5159	Var. 5244	Var. 5329	Var. 5414
170±10	Var. 4820	Var. 4905	Var. 4990	Var. 5075	Var. 5160	Var. 5245	Var. 5330	Var. 5415
175±10	Var. 4821	Var. 4906	Var. 4991	Var. 5076	Var. 5161	Var. 5246	Var. 5331	Var. 5416
180±10	Var. 4822	Var. 4907	Var. 4992	Var. 5077	Var. 5162	Var. 5247	Var. 5332	Var. 5417
190±10	Var. 4823	Var. 4908	Var. 4993	Var. 5078	Var. 5163	Var. 5248	Var. 5333	Var. 5418
25	Var. 4824	Var. 4909	Var. 4994	Var. 5079	Var. 5164	Var. 5249	Var. 5334	Var. 5419
30	Var. 4825	Var. 4910	Var. 4995	Var. 5080	Var. 5165	Var. 5250	Var. 5335	Var. 5420

40	Var. 4826	Var. 4911	Var. 4996	Var. 5081	Var. 5166	Var. 5251	Var. 5336	Var. 5421
50	Var. 4827	Var. 4912	Var. 4997	Var. 5082	Var. 5167	Var. 5252	Var. 5337	Var. 5422
60	Var. 4828	Var. 4913	Var. 4998	Var. 5083	Var. 5168	Var. 5253	Var. 5338	Var. 5423
70	Var. 4829	Var. 4914	Var. 4999	Var. 5084	Var. 5169	Var. 5254	Var. 5339	Var. 5424
75	Var. 4830	Var. 4915	Var. 5000	Var. 5085	Var. 5170	Var. 5255	Var. 5340	Var. 5425
80	Var. 4831	Var. 4916	Var. 5001	Var. 5086	Var. 5171	Var. 5256	Var. 5341	Var. 5426
90	Var. 4832	Var. 4917	Var. 5002	Var. 5087	Var. 5172	Var. 5257	Var. 5342	Var. 5427
100	Var. 4833	Var. 4918	Var. 5003	Var. 5088	Var. 5173	Var. 5258	Var. 5343	Var. 5428
110	Var. 4834	Var. 4919	Var. 5004	Var. 5089	Var. 5174	Var. 5259	Var. 5344	Var. 5429
120	Var. 4835	Var. 4920	Var. 5005	Var. 5090	Var. 5175	Var. 5260	Var. 5345	Var. 5430
125	Var. 4836	Var. 4921	Var. 5006	Var. 5091	Var. 5176	Var. 5261	Var. 5346	Var. 5431
130	Var. 4837	Var. 4922	Var. 5007	Var. 5092	Var. 5177	Var. 5262	Var. 5347	Var. 5432
140	Var. 4838	Var. 4923	Var. 5008	Var. 5093	Var. 5178	Var. 5263	Var. 5348	Var. 5433
150	Var. 4839	Var. 4924	Var. 5009	Var. 5094	Var. 5179	Var. 5264	Var. 5349	Var. 5434
160	Var. 4840	Var. 4925	Var. 5010	Var. 5095	Var. 5180	Var. 5265	Var. 5350	Var. 5435
170	Var. 4841	Var. 4926	Var. 5011	Var. 5096	Var. 5181	Var. 5266	Var. 5351	Var. 5436
175	Var. 4842	Var. 4927	Var. 5012	Var. 5097	Var. 5182	Var. 5267	Var. 5352	Var. 5437
180	Var. 4843	Var. 4928	Var. 5013	Var. 5098	Var. 5183	Var. 5268	Var. 5353	Var. 5438
190	Var. 4844	Var. 4929	Var. 5014	Var. 5099	Var. 5184	Var. 5269	Var. 5354	Var. 5439
200	Var. 4845	Var. 4930	Var. 5015	Var. 5100	Var. 5185	Var. 5270	Var. 5355	Var. 5440

Var. = Variation

Table 9. Exemplary embodiments for the combination of sugar or sugar alcohol and non-ionic surfactant concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

	Sugar or Sugar Alcohol (%)						
Non-Ionic Surfactant (ppm)	14%	15%	16%	17%	18%	19%	20%
10-200	Var. 5441	Var. 5526	Var. 5611	Var. 5696	Var. 5781	Var. 5866	Var. 5951
10-175	Var. 5442	Var. 5527	Var. 5612	Var. 5697	Var. 5782	Var. 5867	Var. 5952
10-150	Var. 5443	Var. 5528	Var. 5613	Var. 5698	Var. 5783	Var. 5868	Var. 5953
10-125	Var. 5444	Var. 5529	Var. 5614	Var. 5699	Var. 5784	Var. 5869	Var. 5954
10-100	Var. 5445	Var. 5530	Var. 5615	Var. 5700	Var. 5785	Var. 5870	Var. 5955
10-90	Var. 5446	Var. 5531	Var. 5616	Var. 5701	Var. 5786	Var. 5871	Var. 5956
10-80	Var. 5447	Var. 5532	Var. 5617	Var. 5702	Var. 5787	Var. 5872	Var. 5957
10-75	Var. 5448	Var. 5533	Var. 5618	Var. 5703	Var. 5788	Var. 5873	Var. 5958
10-70	Var. 5449	Var. 5534	Var. 5619	Var. 5704	Var. 5789	Var. 5874	Var. 5959
10-60	Var. 5450	Var. 5535	Var. 5620	Var. 5705	Var. 5790	Var. 5875	Var. 5960
10-50	Var. 5451	Var. 5536	Var. 5621	Var. 5706	Var. 5791	Var. 5876	Var. 5961
10-25	Var. 5452	Var. 5537	Var. 5622	Var. 5707	Var. 5792	Var. 5877	Var. 5962
25-200	Var. 5453	Var. 5538	Var. 5623	Var. 5708	Var. 5793	Var. 5878	Var. 5963
25-175	Var. 5454	Var. 5539	Var. 5624	Var. 5709	Var. 5794	Var. 5879	Var. 5964
25-150	Var. 5455	Var. 5540	Var. 5625	Var. 5710	Var. 5795	Var. 5880	Var. 5965
25-125	Var. 5456	Var. 5541	Var. 5626	Var. 5711	Var. 5796	Var. 5881	Var. 5966
25-100	Var. 5457	Var. 5542	Var. 5627	Var. 5712	Var. 5797	Var. 5882	Var. 5967
25-90	Var. 5458	Var. 5543	Var. 5628	Var. 5713	Var. 5798	Var. 5883	Var. 5968

25-80	Var. 5459	Var. 5544	Var. 5629	Var. 5714	Var. 5799	Var. 5884	Var. 5969
25-70	Var. 5460	Var. 5545	Var. 5630	Var. 5715	Var. 5800	Var. 5885	Var. 5970
25-60	Var. 5461	Var. 5546	Var. 5631	Var. 5716	Var. 5801	Var. 5886	Var. 5971
25-50	Var. 5462	Var. 5547	Var. 5632	Var. 5717	Var. 5802	Var. 5887	Var. 5972
50-200	Var. 5463	Var. 5548	Var. 5633	Var. 5718	Var. 5803	Var. 5888	Var. 5973
50-175	Var. 5464	Var. 5549	Var. 5634	Var. 5719	Var. 5804	Var. 5889	Var. 5974
50-150	Var. 5465	Var. 5550	Var. 5635	Var. 5720	Var. 5805	Var. 5890	Var. 5975
50-125	Var. 5466	Var. 5551	Var. 5636	Var. 5721	Var. 5806	Var. 5891	Var. 5976
50-90	Var. 5467	Var. 5552	Var. 5637	Var. 5722	Var. 5807	Var. 5892	Var. 5977
50-80	Var. 5468	Var. 5553	Var. 5638	Var. 5723	Var. 5808	Var. 5893	Var. 5978
75-200	Var. 5469	Var. 5554	Var. 5639	Var. 5724	Var. 5809	Var. 5894	Var. 5979
75-175	Var. 5470	Var. 5555	Var. 5640	Var. 5725	Var. 5810	Var. 5895	Var. 5980
75-150	Var. 5471	Var. 5556	Var. 5641	Var. 5726	Var. 5811	Var. 5896	Var. 5981
100-200	Var. 5472	Var. 5557	Var. 5642	Var. 5727	Var. 5812	Var. 5897	Var. 5982
100-175	Var. 5473	Var. 5558	Var. 5643	Var. 5728	Var. 5813	Var. 5898	Var. 5983
50±25	Var. 5474	Var. 5559	Var. 5644	Var. 5729	Var. 5814	Var. 5899	Var. 5984
60±25	Var. 5475	Var. 5560	Var. 5645	Var. 5730	Var. 5815	Var. 5900	Var. 5985
70±25	Var. 5476	Var. 5561	Var. 5646	Var. 5731	Var. 5816	Var. 5901	Var. 5986
75±25	Var. 5477	Var. 5562	Var. 5647	Var. 5732	Var. 5817	Var. 5902	Var. 5987
80±25	Var. 5478	Var. 5563	Var. 5648	Var. 5733	Var. 5818	Var. 5903	Var. 5988
90±25	Var. 5479	Var. 5564	Var. 5649	Var. 5734	Var. 5819	Var. 5904	Var. 5989
100±25	Var. 5480	Var. 5565	Var. 5650	Var. 5735	Var. 5820	Var. 5905	Var. 5990
125±25	Var. 5481	Var. 5566	Var. 5651	Var. 5736	Var. 5821	Var. 5906	Var. 5991
150±25	Var. 5482	Var. 5567	Var. 5652	Var. 5737	Var. 5822	Var. 5907	Var. 5992
175±25	Var. 5483	Var. 5568	Var. 5653	Var. 5738	Var. 5823	Var. 5908	Var. 5993
30±10	Var. 5484	Var. 5569	Var. 5654	Var. 5739	Var. 5824	Var. 5909	Var. 5994
40±10	Var. 5485	Var. 5570	Var. 5655	Var. 5740	Var. 5825	Var. 5910	Var. 5995
50±10	Var. 5486	Var. 5571	Var. 5656	Var. 5741	Var. 5826	Var. 5911	Var. 5996
60±10	Var. 5487	Var. 5572	Var. 5657	Var. 5742	Var. 5827	Var. 5912	Var. 5997
70±10	Var. 5488	Var. 5573	Var. 5658	Var. 5743	Var. 5828	Var. 5913	Var. 5998
75±10	Var. 5489	Var. 5574	Var. 5659	Var. 5744	Var. 5829	Var. 5914	Var. 5999
80±10	Var. 5490	Var. 5575	Var. 5660	Var. 5745	Var. 5830	Var. 5915	Var. 6000
90±10	Var. 5491	Var. 5576	Var. 5661	Var. 5746	Var. 5831	Var. 5916	Var. 6001
100±10	Var. 5492	Var. 5577	Var. 5662	Var. 5747	Var. 5832	Var. 5917	Var. 6002
110±10	Var. 5493	Var. 5578	Var. 5663	Var. 5748	Var. 5833	Var. 5918	Var. 6003
120±10	Var. 5494	Var. 5579	Var. 5664	Var. 5749	Var. 5834	Var. 5919	Var. 6004
125±10	Var. 5495	Var. 5580	Var. 5665	Var. 5750	Var. 5835	Var. 5920	Var. 6005
130±10	Var. 5496	Var. 5581	Var. 5666	Var. 5751	Var. 5836	Var. 5921	Var. 6006
140±10	Var. 5497	Var. 5582	Var. 5667	Var. 5752	Var. 5837	Var. 5922	Var. 6007
150±10	Var. 5498	Var. 5583	Var. 5668	Var. 5753	Var. 5838	Var. 5923	Var. 6008
160±10	Var. 5499	Var. 5584	Var. 5669	Var. 5754	Var. 5839	Var. 5924	Var. 6009
170±10	Var. 5500	Var. 5585	Var. 5670	Var. 5755	Var. 5840	Var. 5925	Var. 6010
175±10	Var. 5501	Var. 5586	Var. 5671	Var. 5756	Var. 5841	Var. 5926	Var. 6011

180±10	Var. 5502	Var. 5587	Var. 5672	Var. 5757	Var. 5842	Var. 5927	Var. 6012
190±10	Var. 5503	Var. 5588	Var. 5673	Var. 5758	Var. 5843	Var. 5928	Var. 6013
25	Var. 5504	Var. 5589	Var. 5674	Var. 5759	Var. 5844	Var. 5929	Var. 6014
30	Var. 5505	Var. 5590	Var. 5675	Var. 5760	Var. 5845	Var. 5930	Var. 6015
40	Var. 5506	Var. 5591	Var. 5676	Var. 5761	Var. 5846	Var. 5931	Var. 6016
50	Var. 5507	Var. 5592	Var. 5677	Var. 5762	Var. 5847	Var. 5932	Var. 6017
60	Var. 5508	Var. 5593	Var. 5678	Var. 5763	Var. 5848	Var. 5933	Var. 6018
70	Var. 5509	Var. 5594	Var. 5679	Var. 5764	Var. 5849	Var. 5934	Var. 6019
75	Var. 5510	Var. 5595	Var. 5680	Var. 5765	Var. 5850	Var. 5935	Var. 6020
80	Var. 5511	Var. 5596	Var. 5681	Var. 5766	Var. 5851	Var. 5936	Var. 6021
90	Var. 5512	Var. 5597	Var. 5682	Var. 5767	Var. 5852	Var. 5937	Var. 6022
100	Var. 5513	Var. 5598	Var. 5683	Var. 5768	Var. 5853	Var. 5938	Var. 6023
110	Var. 5514	Var. 5599	Var. 5684	Var. 5769	Var. 5854	Var. 5939	Var. 6024
120	Var. 5515	Var. 5600	Var. 5685	Var. 5770	Var. 5855	Var. 5940	Var. 6025
125	Var. 5516	Var. 5601	Var. 5686	Var. 5771	Var. 5856	Var. 5941	Var. 6026
130	Var. 5517	Var. 5602	Var. 5687	Var. 5772	Var. 5857	Var. 5942	Var. 6027
140	Var. 5518	Var. 5603	Var. 5688	Var. 5773	Var. 5858	Var. 5943	Var. 6028
150	Var. 5519	Var. 5604	Var. 5689	Var. 5774	Var. 5859	Var. 5944	Var. 6029
160	Var. 5520	Var. 5605	Var. 5690	Var. 5775	Var. 5860	Var. 5945	Var. 6030
170	Var. 5521	Var. 5606	Var. 5691	Var. 5776	Var. 5861	Var. 5946	Var. 6031
175	Var. 5522	Var. 5607	Var. 5692	Var. 5777	Var. 5862	Var. 5947	Var. 6032
180	Var. 5523	Var. 5608	Var. 5693	Var. 5778	Var. 5863	Var. 5948	Var. 6033
190	Var. 5524	Var. 5609	Var. 5694	Var. 5779	Var. 5864	Var. 5949	Var. 6034
200	Var. 5525	Var. 5610	Var. 5695	Var. 5780	Var. 5865	Var. 5950	Var. 6035

Var. = Variation

1. Sugars and Sugar Alcohols

[0161] Advantageously, it was found that the addition of sugar and/or sugar alcohol to furin compositions (*e.g.*, rfurin compositions) increases the storage stability of the composition. For example, as shown in Figures 17 to 20 and 22 to 25, the inclusion of as little as 2% sugar and/or sugar alcohol can increase the storage stability of a furin composition by at least 20%. And the inclusion of 10% sugar and/or sugar alcohol can increase the storage stability of a furin composition by at least 75%. Accordingly, in one aspect of the present disclosure, a storage stable composition of furin (*e.g.*, rfurin) contains a stabilizing amount of sugar and/or sugar alcohol.

[0162] In one embodiment, the storage stable composition of furin (*e.g.*, rfurin) contains monosaccharide sugar. In a particular embodiment, the monosaccharide sugar is selected from the group consisting of a diose sugar, a triose sugar, a tetrose sugar, a pentose sugar, a hexose

sugar, a heptose sugar, and an octose sugar. In a particular embodiment, the sugar is a pentose sugar, a hexose sugar, or a combination thereof. In a specific embodiment, the sugar is a hexose sugar.

[0163] In another embodiment, the storage stable composition of furin (*e.g.*, rfurin) contains a disaccharide sugar. In a particular embodiment, the disaccharide sugar is selected from disaccharide sugars formed from pentose and/or hexose monosaccharides. In another particular embodiment, the sugar is selected from disaccharide sugars formed from hexose monosaccharides. In one embodiment, the sugar is sucrose, trehalose, or a combination thereof. In one specific embodiment, the sugar is sucrose. In another specific embodiment, the sugar is trehalose. In one embodiment, the sugar is formulated as trehalose dihydrate.

[0164] In another embodiment, the storage stable composition of furin (*e.g.*, rfurin) contains a sugar alcohol. In a particular embodiment, the sugar alcohol is selected from glycol, glycerol, erythritol, threitol, ribitol, fucitol, iditol, volmitol, isomalt, maltitol, lactitol, mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol. In another particular embodiment, the sugar alcohol is mannitol.

[0165] In yet another embodiment, the stable composition of furin (*e.g.*, rfurin) contains a mixture of sugar and sugar alcohol. In one embodiment, the mixture contains at least two of a monosaccharide, a disaccharide, and a sugar alcohol. In another embodiment, the mixture contains at least two of a pentose sugar, a hexose sugar, a disaccharide formed from pentose and/or hexose monosaccharides, and a sugar alcohol. In another embodiment, the mixture contains at least two of sucrose, trehalose, and mannitol.

[0166] In one embodiment, the sugar or sugar alcohol is present at a concentration of from 2% to 20%, 2% to 17.5%, 2% to 15%, 2% to 12.5%, 2% to 10%, 2% to 9%, 2% to 8%, 2% to 7%, 5% to 20%, 5% to 17.5%, 5% to 15%, 5% to 12.5%, 5% to 10%, 7.5% to 20%, 7.5% to 17.5%, 7.5% to 15%, 7.5% to 12.5%, 10% to 20%, 10% to 17.5%, 10% to 15%, 4±2%, 5±2%, 6±2%, 7±2%, 8±2%, 9±2%, 10±2%, 11±2%, 12±2%, 13±2%, 14±2%, 15±2%, 16±2%, 17±2%, 18±2%, 3±1%, 4±1%, 5±1%, 6±1%, 7±1%, 8±1%, 9±1%, 10±1%, 11±1%, 12±1%, 13±1%, 14±1%, 15±1%, 16±1%, 17±1%, 18±1%, 19±1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%. In one embodiment, the sugar or sugar alcohol

is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose.

[0167] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 mM to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 2% to 20% sugar or sugar alcohol, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 10 ppm to 200 ppm non-ionic surfactant. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0168] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 2% to 20% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0169] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 2% to 20% trehalose, from 10 ppm to 100 ppm non-ionic surfactant, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0170] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0171] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; a combination of trehalose and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0172] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 20% sugar or sugar alcohol, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 10 ppm to 200 ppm non-ionic surfactant. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0173] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 mM to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 20% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, from 10 to 200

mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0174] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 mM to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 20% trehalose, from 10 ppm to 100 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0175] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0176] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of trehalose and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific

embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0177] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; 10±5% sugar or sugar alcohol, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 10 to 200 ppm non-ionic surfactant. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% sugar or sugar alcohol. In another specific embodiment, the composition contains 10±1% sugar or sugar alcohol. In another specific embodiment, the composition contains 10% sugar or sugar alcohol.

[0178] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; 10±5% sugar or sugar alcohol, from 10 to 100 ppm non-ionic surfactant, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% sugar or sugar alcohol. In another specific embodiment, the composition contains 10±1% sugar or sugar alcohol. In another specific embodiment, the composition contains 10% sugar or sugar alcohol.

[0179] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; 10±5% trehalose, from 10 to 100 ppm non-ionic surfactant, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In

a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% trehalose. In another specific embodiment, the composition contains 10±1% trehalose. In another specific embodiment, the composition contains 10% trehalose.

[0180] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0181] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of trehalose and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0182] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 10±5% sugar or sugar alcohol, 91 mM buffering agent, and a pH of 6.0±0.2. In one embodiment, the storage stable furin composition further comprises from 10 to 200 ppm non-ionic surfactant. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% sugar or sugar alcohol. In another specific embodiment, the

composition contains 10±1% sugar or sugar alcohol. In another specific embodiment, the composition contains 10% sugar or sugar alcohol.

[0183] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 10±5% sugar or sugar alcohol, 75 ppm non-ionic surfactant, 91 mM buffering agent, and a pH from of 6.0±0.2. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% sugar or sugar alcohol. In another specific embodiment, the composition contains 10±1% sugar or sugar alcohol. In another specific embodiment, the composition contains 10% sugar or sugar alcohol.

[0184] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 10±5% trehalose, 75 ppm non-ionic surfactant, 91 mM buffering agent, and a pH of 6.0±0.2. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In another specific embodiment, the composition contains 10±2% trehalose. In another specific embodiment, the composition contains 10±1% trehalose. In another specific embodiment, the composition contains 10% trehalose.

[0185] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, 91 mM buffering agent, and a pH of 6.0±0.2. In a specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0186] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; a combination of trehalose and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, 91 mM buffering

agent, and a pH of 6.0±0.2. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0187] In some embodiments, stabilizing agents used in the formulations of the present disclosure are selected from a group that includes, without limitation: sucrose, trehalose, mannitol, raffinose, and arginine. These agents are present in the formulations of the present invention in an amount of from 0.1% to 20%. In certain embodiments, the stabilizing agent is present in an amount of from 5% to 15%, or about 10%. In further embodiments, formulations of the present disclosure include stabilizing agents in an amount of from 0.5% to 19%, 1% to 18%, 1.5% to 17%, 2.0% to 16%, 2.5% to 15%, 3.0% to 14%, 3.5% to 13%, 4.0% to 12%, 4.5% to 11%, 5.0% to 10%, 5.5% to 9%, or 6.0% to 8%. Certain formulations include mannitol, sucrose, and/or trehalose in combination with one or more of any other formulation components disclosed herein.

2. Non-Ionic Surfactants

[0188] Advantageously, it was found that the addition of sugar non-ionic surfactant to furin compositions (*e.g.*, rfurin compositions) increases the stability of the composition to mechanical stress. For example, as shown in Figures 31 to 42, the inclusion of as little as 10 ppm non-ionic surfactant can increase the stability of a furin composition subjected to mechanical stress by at least 25%. And the inclusion of 50 ppm non-ionic surfactant can increase the stability of a furin composition subjected to mechanical stress by at least 40%. Accordingly, in one aspect of the present disclosure, a storage stable composition of furin (*e.g.*, rfurin) contains a stabilizing amount of non-ionic surfactant.

[0189] In one embodiment, storage stable compositions of furin (*e.g.*, rfurin) are provided which contain a non-ionic surfactant selected from a non-ionic water soluble monoglyceride, a non-ionic water soluble diglyceride, a non-ionic water soluble triglyceride, a non-ionic water soluble monofatty acid esters of polyethyelene glycol, a non-ionic water soluble difatty acid esters of polyethyelene glycol, a non-ionic water soluble sorbitan fatty acid ester, a non-ionic polyglycolyzed glyceride, a non-ionic water soluble triblock copolymer, and a combination thereof. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty

acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0190] In one embodiment, the non-ionic surfactant is present at a concentration of from 10 to 200 ppm, 10 to 175 ppm, 10 to 150 ppm, 10 to 125 ppm, 10 to 100 ppm, 10 to 90 ppm, 10 to 80 ppm, 10 to 75 ppm, 10 to 70 ppm, 10 to 60 ppm, 10 to 50 ppm, 10 to 25 ppm, 25 to 200 ppm, 25 to 175 ppm, 25 to 150 ppm, 25 to 125 ppm, 25 to 100 ppm, 25 to 90 ppm, 25 to 80 ppm, 25 to 70 ppm, 25 to 60 ppm, 25 to 50 ppm, 50 to 200 ppm, 50 to 175 ppm, 50 to 150 ppm, 50 to 125 ppm, 50 to 90 ppm, 50 to 80 ppm, 75 to 200 ppm, 75 to 175 ppm, 75 to 150 ppm, 100 to 200 ppm, 100 to 175 ppm, 50±25 ppm, 60±25 ppm, 70±25 ppm, 75±25 ppm, 80±25 ppm, 90±25 ppm, 100±25 ppm, 125±25 ppm, 150±25 ppm, 175±25 ppm, 30±10 ppm, 40±10 ppm, 50±10 ppm, 60±10 ppm, 70±10 ppm, 75±10 ppm, 80±10 ppm, 90±10 ppm, 100±10 ppm, 110±10 ppm, 120±10 ppm, 125±10 ppm, 130±10 ppm, 140±10 ppm, 150±10 ppm, 160±10 ppm, 170±10 ppm, 175±10 ppm, 180±10 ppm, 190±10 ppm, 25 ppm, 30 ppm, 40 ppm, 50 ppm, 60 ppm, 70 ppm, 75 ppm, 80 ppm, 90 ppm, 100 ppm, 110 ppm, 120 ppm, 125 ppm, 130 ppm, 140 ppm, 150 ppm, 160 ppm, 170 ppm, 175 ppm, 180 ppm, 190 ppm, or 200 ppm. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0191] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 mM to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0192] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 2% to 10%

sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0193] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; from 2% to 10% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic water soluble sorbitan fatty acid ester, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0194] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In yet another specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester and the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0195] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium; a combination of sugar or sugar alcohol and a non-ionic water soluble sorbitan fatty acid ester selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0196] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 10 ppm to 200 ppm non-ionic surfactant, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0197] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 mM to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 10% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition

is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0198] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 mM to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 10% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic water soluble sorbitan fatty acid ester, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0199] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In yet another specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester and the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0200] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 100 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic water soluble sorbitan fatty acid ester selected from variations 1 to 6035 found in Table 1 to Table 9, from 10 mM to 200 mM buffering agent, and a

pH from 5.5 to 7.5. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0201] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; 75±25% non-ionic surfactant, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75±5 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75 ppm non-ionic surfactant.

[0202] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 10% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0.

In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75±5 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75 ppm non-ionic surfactant.

[0203] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; from 2% to 10% sugar or sugar alcohol, 75±25 ppm non-ionic water soluble sorbitan fatty acid ester, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the composition contains 75±5 ppm non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the composition contains 75 ppm non-ionic water soluble sorbitan fatty acid ester.

[0204] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In yet another specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester and the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In

another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0205] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium; a combination of sugar or sugar alcohol and non-ionic water soluble sorbitan fatty acid ester selected from variations 1 to 6035 found in Table 1 to Table 9, from 90±25 mM buffering agent, and a pH from 5.5 to 7.5. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0206] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 75±25% non-ionic surfactant, 91 mM buffering agent, and a pH of 6.0±0.2. In one embodiment, the storage stable furin composition further comprises from 2% to 10% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75±5 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75 ppm non-ionic surfactant.

[0207] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 10% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, 91 mM buffering agent, and a pH from of 6.0±0.2. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific

embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75±5 ppm non-ionic surfactant. In another specific embodiment, the composition contains 75 ppm non-ionic surfactant.

[0208] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; 10% sugar or sugar alcohol, 75±25 ppm non-ionic water soluble sorbitan fatty acid ester, 91 mM buffering agent, and a pH of 6.0±0.2. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin. In one specific embodiment, the composition contains 75±15 ppm non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the composition contains 75±5 ppm non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the composition contains 75 ppm non-ionic water soluble sorbitan fatty acid ester.

[0209] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; a combination of sugar or sugar alcohol and non-ionic surfactant selected from variations 1 to 6035 found in Table 1 to Table 9, 91 mM buffering agent, and a pH of 6.0±0.2. In a specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In another specific embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In yet another specific embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester and the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0210] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190 mM of a pharmaceutically acceptable salt, 0.9 mM calcium; a combination of sugar or sugar alcohol and non-ionic water soluble sorbitan fatty acid ester selected from variations 1 to 6035 found in Table 1 to Table 9, 91 mM buffering agent, and a pH of 6.0±0.2. In a specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In another specific embodiment, the sugar or sugar alcohol is trehalose. In yet another specific embodiment, the non-ionic water soluble sorbitan fatty acid ester is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0211] The furin (*e.g.*, rfurin) compositions of the present invention also preferably include a surfactant, preferably a non-ionic surfactant, and preferably in an amount from 0.1 ppm to 150 ppm, or from 65 ppm to 80 ppm, or at about 75 ppm. In further embodiments, the furin (*e.g.*, rfurin) compositions include a surfactant in an amount of from 0.5 ppm to 140 ppm, 1.0 ppm to 130 ppm, 10 ppm to 120 ppm, 20 ppm to 110 ppm, 30 ppm to 100 ppm, 40 ppm to 95 ppm, 50 ppm to 90 ppm, 55 ppm to 85 ppm, 60 ppm to 80 ppm, or 70 ppm to 75 ppm. In certain embodiments, the surfactant is chosen from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, pluronic polyols, glycerol, glucamides (such as Mega 8), tritons, and Brij 35 (polyoxyethylene 23 lauryl ether). Several grades of pluronic polyols (sold under the trade name Pluronic, manufactured by the BASF Wyandotte Corporation) are available. These polyols, of diversified molecular weight (from 1,000 to over 16,000) and physicochemical properties have been used as surfactants. Pluronic F-38, of a molecular weight of 5,000 and Pluronic F-68, molecular weight 9,000, both contain (by weight) 80 per cent hydrophilic polyoxyethylene groups and 20 percent hydrophobic polyoxypropylene groups. In one embodiment, the surfactant is polysorbate 80. In a particular embodiment, the polysorbate 80 is vegetable-derived polysorbate 80.

B. Pharmaceutically Acceptable Salts

[0212] The stabilized compositions of furin (*e.g.*, rfurin) provided herein generally include a pharmaceutically acceptable salt at a concentration tolerated by the furin polypeptide during storage. In one embodiment, the pharmaceutically acceptable salt is a chloride salt. In a specific

embodiment, the pharmaceutically acceptable salt is a monovalent chloride salt. In a more specific embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof.

[0213] In one embodiment, the concentration of pharmaceutically acceptable salt in a stabilized furin (*e.g.*, rfurin) composition provided herein is from 10 mM to 500 mM. In another embodiment, the concentration of pharmaceutically acceptable salt is from 100 mM to 300 mM. In another embodiment, the concentration of pharmaceutically acceptable salt is from 150 mM to 250 mM. In yet other embodiments, the concentration of pharmaceutically acceptable salt in the stabilized furin (*e.g.*, rfurin) compositions provided herein is selected from variations 6036 to 6180 found in Table 10.

Table 10. Exemplary pharmaceutically acceptable salt concentrations useful for the stabilization of furin (*e.g.*, rfurin) compositions.

10 mM to 500 mM	Var. 6036	140±5 mM	Var. 6085	179 mM	Var. 6134
100 mM to 300 mM	Var. 6037	145±5 mM	Var. 6086	180 mM	Var. 6135
150 mM to 250 mM	Var. 6038	150±5 mM	Var. 6087	181 mM	Var. 6136
50 mM to 500 mM	Var. 6039	155±5 mM	Var. 6088	182 mM	Var. 6137
50 mM to 450 mM	Var. 6040	160±5 mM	Var. 6089	183 mM	Var. 6138
50 mM to 400 mM	Var. 6041	165±5 mM	Var. 6090	184 mM	Var. 6139
100 to 400 mM	Var. 6042	170±5 mM	Var. 6091	185 mM	Var. 6140
100 mM to 350 mM	Var. 6043	175±5 mM	Var. 6092	186 mM	Var. 6141
100 mM to 250 mM	Var. 6044	180±5 mM	Var. 6093	187 mM	Var. 6142
100 mM to 200 mM	Var. 6045	185±5 mM	Var. 6094	188 mM	Var. 6143
150 mM to 400 mM	Var. 6046	186±5 mM	Var. 6095	189 mM	Var. 6144
150 mM to 350 mM	Var. 6047	187±5 mM	Var. 6096	190 mM	Var. 6145
150 mM to 300 mM	Var. 6048	188±5 mM	Var. 6097	191 mM	Var. 6146
150 mM to 250 mM	Var. 6049	189±5 mM	Var. 6098	192 mM	Var. 6147
150 mM to 200 mM	Var. 6050	190±5 mM	Var. 6099	193 mM	Var. 6148
175 mM to 225 mM	Var. 6051	191±5 mM	Var. 6100	194 mM	Var. 6149
175 mM to 200 mM	Var. 6052	192±5 mM	Var. 6101	195 mM	Var. 6150
100±25 mM	Var. 6053	193±5 mM	Var. 6102	196 mM	Var. 6151
150±25 mM	Var. 6054	194±5 mM	Var. 6103	197 mM	Var. 6152
200±25 mM	Var. 6055	195±5 mM	Var. 6104	198 mM	Var. 6153
250±25 mM	Var. 6056	196±5 mM	Var. 6105	199 mM	Var. 6154
300±25 mM	Var. 6057	197±5 mM	Var. 6106	200 mM	Var. 6155
350±25 mM	Var. 6058	198±5 mM	Var. 6107	201 mM	Var. 6156
400±25 mM	Var. 6059	199±5 mM	Var. 6108	202 mM	Var. 6157
450±25 mM	Var. 6060	200±5 mM	Var. 6109	203 mM	Var. 6158

190±150 mM	Var. 6061	205±5 mM	Var. 6110	204 mM	Var. 6159
190±125 mM	Var. 6062	210±5 mM	Var. 6111	205 mM	Var. 6160
190±100 mM	Var. 6063	215±5 mM	Var. 6112	206 mM	Var. 6161
190±90 mM	Var. 6064	220±5 mM	Var. 6113	207 mM	Var. 6162
190±80 mM	Var. 6065	225±5 mM	Var. 6114	208 mM	Var. 6163
190±70 mM	Var. 6066	230±5 mM	Var. 6115	209 mM	Var. 6164
190±60 mM	Var. 6067	235±5 mM	Var. 6116	210 mM	Var. 6165
190±50 mM	Var. 6068	240±5 mM	Var. 6117	211 mM	Var. 6166
190±40 mM	Var. 6069	245±5 mM	Var. 6118	212 mM	Var. 6167
190±30 mM	Var. 6070	250±5 mM	Var. 6119	213 mM	Var. 6168
190±25 mM	Var. 6071	255±5 mM	Var. 6120	214 mM	Var. 6169
190±20 mM	Var. 6072	260±5 mM	Var. 6121	215 mM	Var. 6170
190±15 mM	Var. 6073	265±5 mM	Var. 6122	216 mM	Var. 6171
190±10 mM	Var. 6074	270±5 mM	Var. 6123	217 mM	Var. 6172
190±5 mM	Var. 6075	275±5 mM	Var. 6124	218 mM	Var. 6173
190±2 mM	Var. 6076	280±5 mM	Var. 6125	219 mM	Var. 6174
100±5 mM	Var. 6077	285±5 mM	Var. 6126	220 mM	Var. 6175
105±5 mM	Var. 6078	290±5 mM	Var. 6127	221 mM	Var. 6176
110±5 mM	Var. 6079	295±5 mM	Var. 6128	222 mM	Var. 6177
115±5 mM	Var. 6080	300±5 mM	Var. 6129	223 mM	Var. 6178
120±5 mM	Var. 6081	175 mM	Var. 6130	224 mM	Var. 6179
125±5 mM	Var. 6082	176 mM	Var. 6131	225 mM	Var. 6180
130±5 mM	Var. 6083	177 mM	Var. 6132		
135±5 mM	Var. 6084	178 mM	Var. 6133		

Var. = Variation

[0214] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.5 mM to 5 mM calcium, from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the

pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0215] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 10 ppm to 200 ppm non-ionic surfactant. In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0216] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another

embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0217] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.5 mM to 5 mM calcium, from 2% to 10% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0218] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.5 mM to 2 mM calcium, 10±5% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the

pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In one embodiment, the concentration of the buffering agent is 90±25 mM. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0219] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises a pharmaceutically acceptable salt at a concentration selected from variations 6036 to 6180 found in Table 10, from 0.9 mM calcium, 10% sugar or sugar alcohol, 75 ppm non-ionic surfactant, from 91 mM buffering agent, and a pH of 6.0±0.2. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0220] In some embodiments, monovalent chloride salts, such as sodium chloride and potassium chloride, are used in formulations of the present disclosure. Although the formulation component comprising monovalent chloride salts is described primarily in terms of sodium chloride, it will be appreciated that any monovalent chloride salt, including potassium chloride, may be used in accordance with the descriptions herein for sodium chloride. In certain embodiments, sodium chloride is included in the present formulations at an amount of from 50 to 500 mM. In other embodiments, sodium chloride is included in the formulations at an amount of

from 100 to 300 mM, from 150 to 250 mM, or at about 190 mM. In further embodiments, sodium chloride is included in the present formulations in an amount of from 100 to 300 mM, 110 to 280 mM, 120 to 260 mM, 130 to 240 mM, 140 to 220 mM, 150 to 200 mM, or 160 to 180 mM. In a specific embodiment, the formulation includes 190 mM sodium chloride in combination with one or more of any other formulation components disclosed herein.

C. Buffering Agents

[0221] Advantageously, it was found that furin (*e.g.*, rfurin) compositions are stabilized at pH 6.0 to 7.0. For example, it is shown in Figures 11 and 12 that furin compositions formulated at pH 5.5 are stabilized as compared to furin compositions formulated at pH 5.0. Also shown is that furin compositions formulated at pH 6.0 are further stabilized as compared to compositions formulated at pH 5.5. Furthermore, as shown in Figure 17, furin (*e.g.*, rfurin) compositions formulated at pH 7.0 have similar stability to compositions formulated at pH 6.0.

[0222] Accordingly, in certain embodiments, the stabilized furin (*e.g.*, rfurin) compositions provided herein are formulated at a pH from 5.5 to 7.5. In a specific embodiment, a stabilized furin (*e.g.*, rfurin) composition is formulated at a pH from 6.0 to 7.0. In another specific embodiment, a stabilized furin composition is formulated at pH 6.0±0.2. In a more specific embodiment, a stabilized furin composition is formulated at pH 6.0. In yet other embodiments, a stabilized furin composition is formulated at pH selected from variations 6181 to 6403 found in Table 11.

Table 11. Exemplary pH ranges useful for the stabilization of furin (*e.g.*, rfurin) compositions.

5.5-8.0	Var. 6181	5.7-6.3	Var. 6237	6.0-6.7	Var. 6293	5.9	Var. 6349
5.5-7.9	Var. 6182	5.7-6.2	Var. 6238	6.0-6.6	Var. 6294	6	Var. 6350
5.5-7.8	Var. 6183	5.7-6.1	Var. 6239	6.0-6.5	Var. 6295	6.1	Var. 6351
5.5-7.6	Var. 6184	5.7-6.0	Var. 6240	6.0-6.4	Var. 6296	6.2	Var. 6352
5.5-7.5	Var. 6185	5.8-8.0	Var. 6241	6.0-6.3	Var. 6297	6.3	Var. 6353
5.5-7.4	Var. 6186	5.8-7.9	Var. 6242	6.0-6.2	Var. 6298	6.4	Var. 6354
5.5-7.3	Var. 6187	5.8-7.8	Var. 6243	6.0-6.1	Var. 6299	6.5	Var. 6355
5.5-7.2	Var. 6188	5.8-7.6	Var. 6244	5.7±0.2	Var. 6300	6.6	Var. 6356
5.5-7.1	Var. 6189	5.8-7.5	Var. 6245	5.8±0.2	Var. 6301	6.7	Var. 6357
5.5-7.0	Var. 6190	5.8-7.4	Var. 6246	5.9±0.2	Var. 6302	6.8	Var. 6358
5.5-6.9	Var. 6191	5.8-7.3	Var. 6247	6.0±0.2	Var. 6303	6.9	Var. 6359
5.5-6.8	Var. 6192	5.8-7.2	Var. 6248	6.1±0.2	Var. 6304	7	Var. 6360
5.5-6.7	Var. 6193	5.8-7.1	Var. 6249	6.2±0.2	Var. 6305	7.1	Var. 6361

5.5-6.6	Var. 6194	5.8-7.0	Var. 6250	6.3±0.2	Var. 6306	7.2	Var. 6362
5.5-6.5	Var. 6195	5.8-6.9	Var. 6251	6.4±0.2	Var. 6307	7.3	Var. 6363
5.5-6.4	Var. 6196	5.8-6.8	Var. 6252	6.5±0.2	Var. 6308	7.4	Var. 6364
5.5-6.3	Var. 6197	5.8-6.7	Var. 6253	6.6±0.2	Var. 6309	7.5	Var. 6365
5.5-6.2	Var. 6198	5.8-6.6	Var. 6254	6.7±0.2	Var. 6310	7.6	Var. 6366
5.5-6.1	Var. 6199	5.8-6.5	Var. 6255	6.8±0.2	Var. 6311	7.7	Var. 6367
5.5-6.0	Var. 6200	5.8-6.4	Var. 6256	6.9±0.2	Var. 6312	7.8	Var. 6368
5.6-8.0	Var. 6201	5.8-6.3	Var. 6257	7.0±0.2	Var. 6313	7.9	Var. 6369
5.6-7.9	Var. 6202	5.8-6.2	Var. 6258	7.1±0.2	Var. 6314	8	Var. 6370
5.6-7.8	Var. 6203	5.8-6.1	Var. 6259	7.2±0.2	Var. 6315	6.0±0.3	Var. 6371
5.6-7.6	Var. 6204	5.8-6.0	Var. 6260	7.3±0.2	Var. 6316	6.0±0.4	Var. 6372
5.6-7.5	Var. 6205	5.9-8.0	Var. 6261	7.4±0.2	Var. 6317	6.0±0.5	Var. 6373
5.6-7.4	Var. 6206	5.9-7.9	Var. 6262	7.5±0.2	Var. 6318	6.1±0.3	Var. 6374
5.6-7.3	Var. 6207	5.9-7.8	Var. 6263	7.6±0.2	Var. 6319	6.1±0.4	Var. 6375
5.6-7.2	Var. 6208	5.9-7.6	Var. 6264	7.7±0.2	Var. 6320	6.1±0.5	Var. 6376
5.6-7.1	Var. 6209	5.9-7.5	Var. 6265	7.8±0.2	Var. 6321	6.2±0.3	Var. 6377
5.6-7.0	Var. 6210	5.9-7.4	Var. 6266	5.6±0.1	Var. 6322	6.2±0.4	Var. 6378
5.6-6.9	Var. 6211	5.9-7.3	Var. 6267	5.7±0.1	Var. 6323	6.2±0.5	Var. 6379
5.6-6.8	Var. 6212	5.9-7.2	Var. 6268	5.8±0.1	Var. 6324	6.3±0.3	Var. 6380
5.6-6.7	Var. 6213	5.9-7.1	Var. 6269	5.9±0.1	Var. 6325	6.3±0.4	Var. 6381
5.6-6.6	Var. 6214	5.9-7.0	Var. 6270	6.0±0.1	Var. 6326	6.3±0.5	Var. 6382
5.6-6.5	Var. 6215	5.9-6.9	Var. 6271	6.1±0.1	Var. 6327	6.4±0.3	Var. 6383
5.6-6.4	Var. 6216	5.9-6.8	Var. 6272	6.2±0.1	Var. 6328	6.4±0.4	Var. 6384
5.6-6.3	Var. 6217	5.9-6.7	Var. 6273	6.3±0.1	Var. 6329	6.4±0.5	Var. 6385
5.6-6.2	Var. 6218	5.9-6.6	Var. 6274	6.4±0.1	Var. 6330	6.5±0.3	Var. 6386
5.6-6.1	Var. 6219	5.9-6.5	Var. 6275	6.5±0.1	Var. 6331	6.5±0.4	Var. 6387
5.6-6.0	Var. 6220	5.9-6.4	Var. 6276	6.6±0.1	Var. 6332	6.5±0.5	Var. 6388
5.7-8.0	Var. 6221	5.9-6.3	Var. 6277	6.7±0.1	Var. 6333	6.6±0.3	Var. 6389
5.7-7.9	Var. 6222	5.9-6.2	Var. 6278	6.8±0.1	Var. 6334	6.6±0.4	Var. 6390
5.7-7.8	Var. 6223	5.9-6.1	Var. 6279	6.9±0.1	Var. 6335	6.6±0.5	Var. 6391
5.7-7.6	Var. 6224	5.9-6.0	Var. 6280	7.0±0.1	Var. 6336	6.7±0.3	Var. 6392
5.7-7.5	Var. 6225	6.0-8.0	Var. 6281	7.1±0.1	Var. 6337	6.7±0.4	Var. 6393
5.7-7.4	Var. 6226	6.0-7.9	Var. 6282	7.2±0.1	Var. 6338	6.7±0.5	Var. 6394
5.7-7.3	Var. 6227	6.0-7.8	Var. 6283	7.3±0.1	Var. 6339	6.8±0.3	Var. 6395
5.7-7.2	Var. 6228	6.0-7.6	Var. 6284	7.4±0.1	Var. 6340	6.8±0.4	Var. 6396
5.7-7.1	Var. 6229	6.0-7.5	Var. 6285	7.5±0.1	Var. 6341	6.8±0.5	Var. 6397
5.7-7.0	Var. 6230	6.0-7.4	Var. 6286	7.6±0.1	Var. 6342	6.9±0.3	Var. 6398
5.7-6.9	Var. 6231	6.0-7.3	Var. 6287	7.7±0.1	Var. 6343	6.9±0.4	Var. 6399
5.7-6.8	Var. 6232	6.0-7.2	Var. 6288	7.8±0.1	Var. 6344	6.9±0.5	Var. 6400
5.7-6.7	Var. 6233	6.0-7.1	Var. 6289	5.5	Var. 6345	7.0±0.3	Var. 6401
5.7-6.6	Var. 6234	6.0-7.0	Var. 6290	5.6	Var. 6346	7.0±0.4	Var. 6402
5.7-6.5	Var. 6235	6.0-6.9	Var. 6291	5.7	Var. 6347	7.0±0.5	Var. 6403
5.7-6.4	Var. 6236	6.0-6.8	Var. 6292	5.8	Var. 6348		

Var. = Variation

[0223] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0224] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the storage stable furin composition further comprises from 10 ppm to 200 ppm non-ionic surfactant. In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0225] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0226] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 10% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0227] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, from 2% to 10% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0228] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, 10±5% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, from 10 to 200 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a

specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0229] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, 10±5% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, from 90±25 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0230] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 191 mM of a pharmaceutically acceptable salt, 0.9 mM calcium, 10% sugar or sugar alcohol, 75 ppm non-ionic surfactant, 91 mM buffering agent, and a pH selected from variations 6181 to 6403 found in Table 11. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0231] In one embodiment, the stabilized furin (*e.g.*, rfurin) compositions provided herein are formulated at an appropriate pH using one or more buffering agents. In one embodiment, the one or more buffering agent is selected from histidine, imidazole, phosphate, citrate, Tris, acetate (*e.g.*, acetic acid), BIS-Tris Propane, PIPES, MOPS, HEPES, MES, ACES, and a combination

thereof. In a particular embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES.

[0232] Buffering agent is present in the stabilized furin (*e.g.*, rfurin) compositions at a concentration suitable to maintain the pH of the composition during storage over a period of time (*e.g.*, weeks, months, or years). In one embodiment, the concentration of buffering agent in the formulation is from 10 mM to 300 mM. In another embodiment, the concentration of buffering agent in the formulation is between 10 mM to 200 mM. In a specific embodiment, the concentration of buffering agent in the formulation is 90±25 mM. In yet other embodiments, the concentration of buffering agent in the composition is selected from variations 6404 to 6469 found in Table 12.

Table 12. Exemplary buffering agent concentrations (mM) useful for the stabilization of furin (*e.g.*, rfurin) compositions.

10-300	Var. 6404	50-200	Var. 6426	91±2	Var. 6448
10-275	Var. 6405	50-175	Var. 6427	80	Var. 6449
10-250	Var. 6406	50-150	Var. 6428	81	Var. 6450
10-225	Var. 6407	50-125	Var. 6429	82	Var. 6451
10-200	Var. 6408	50-100	Var. 6430	83	Var. 6452
10-175	Var. 6409	75-300	Var. 6431	84	Var. 6453
10-150	Var. 6410	75-275	Var. 6432	85	Var. 6454
10-125	Var. 6411	75-250	Var. 6433	86	Var. 6455
10-100	Var. 6412	75-225	Var. 6434	87	Var. 6456
25-300	Var. 6413	75-200	Var. 6435	88	Var. 6457
25-275	Var. 6414	75-175	Var. 6436	89	Var. 6458
25-250	Var. 6415	75-150	Var. 6437	90	Var. 6459
25-225	Var. 6416	75-125	Var. 6438	91	Var. 6460
25-200	Var. 6417	75-100	Var. 6439	92	Var. 6461
25-175	Var. 6418	90±75	Var. 6440	93	Var. 6462
25-150	Var. 6419	90±50	Var. 6441	94	Var. 6463
25-125	Var. 6420	90±25	Var. 6442	95	Var. 6464
25-100	Var. 6421	90±10	Var. 6443	96	Var. 6465
50-300	Var. 6422	90±5	Var. 6444	97	Var. 6466
50-275	Var. 6423	90±2	Var. 6445	98	Var. 6467
50-250	Var. 6424	91±10	Var. 6446	99	Var. 6468
50-225	Var. 6425	91±5	Var. 6447	100	Var. 6469

Var. = Variation

[0233] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 10 ppm to

200 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 2% to 20% sugar or sugar alcohol. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0234] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the storage stable furin composition further comprises from 10 ppm to 200 ppm non-ionic surfactant. In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0235] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 20% sugar or sugar alcohol, from 10 ppm to 200 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20)

sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0236] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 500 mM of a pharmaceutically acceptable salt, from 0.5 mM to 5 mM calcium, from 2% to 10% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0237] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, from 2% to 10% sugar or sugar alcohol, from 10 ppm to 100 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5.

In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0238] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises from 50 to 300 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, 10±5% sugar or sugar alcohol, 75±25 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0239] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 190±50 mM of a pharmaceutically acceptable salt, from 0.5 mM to 2 mM calcium, 10±5% sugar or sugar

alcohol, 75±25 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0240] In one embodiment, a stabilized furin (*e.g.*, rfurin) composition comprises 191 mM of a pharmaceutically acceptable salt, 0.9 mM calcium, 10% sugar or sugar alcohol, 75 ppm non-ionic surfactant, buffering agent at a concentration selected from variations 6404 to 6469 found in Table 12, and a pH from 5.5 to 7.5. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) and the sugar or sugar alcohol is trehalose. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES. In one embodiment, the pH of the composition is from 5.5 to 7.0. In another embodiment, the pH of the composition is from 5.5 to 6.5. In another embodiment, the pH of the composition is 6.0±0.2. In a specific embodiment, the pH of the composition is 6.0. In a specific embodiment, the composition contains from 8,000 U/mL to 500,000 U/mL rfurin.

[0241] Buffers may also be present in formulations of the invention in combination with one or more of any other formulation components described herein. As shown in the Examples, the highly stabilized formulations of the present invention show increased stability at pH 6.0. In certain embodiments, the pH of the highly stabilized formulations should preferably be maintained in the range of from 6.0 to 8.0, or at a pH of about 6.0. The buffering agent can be any physiologically acceptable chemical entity or combination of chemical entities which have the capacity to act as buffers, including, without limitation: histidine, imidazole, phosphate, citrate, Tris, Acetate, BIS-Tris Propane, PIPES, MOPS, HEPES, MES, and ACES. The full chemical designations of many of these buffering agents are listed in Table 1 below. In certain embodiments, if calcium is present in the formulation at a concentration above about 5 mM, phosphate is not used as a buffering agent. In some embodiments, the buffering agent is included in a concentration of from 10 mM to 200 mM, or 10 to 100 mM, or 30-60 mM, or about 46 mM. In further embodiments, an individual buffering agent is included in a concentration of from 15 to 95 mM, 20 to 90 mM, 25 to 85 mM, 30 to 80 mM, 35 to 75 mM, 40 to 70 mM, 45 to 65 mM, or 50 to 60 mM. In certain embodiments, the formulation contains two buffering agents.

Table 13. Exemplary Buffering Agents

Tris	tris-(hydroxymethyl)-aminomethane
BIS-Tris Propane	1,3-bis-[tris-(hydroxy-methyl)methylamino]-propane
PIPES	piperazine-N,N'-bis-(2-ethanesulfonic acid)
MOPS	3-(N-morpholino) propanesulfonic acid
HEPES	N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid
MES	2-(N-morpholino) ethanesulfonic acid
ACES	N-2-acetamido-2-aminoethanesulfonic acid

[0242] In certain aspects the present formulations include a carboxylic acid in combination with one or more of the formulation components described herein. In further aspects, the carboxylic acid is preferably acetic acid (*e.g.*, acetate). In certain embodiments, the formulation includes from 20 mM to 100 mM acetic acid, or from 30 mM to 50 mM, or about 45 mM acetic acid or any other carboxylic acid. In further embodiments, the formulation includes from 25 mM to 90 mM, 30 mM to 80 mM, 35 mM to 70 mM, 40 mM to 60 mM, or 45 mM to 50 mM acetic acid or any other carboxylic acid.

D. Additional Formulation Components

[0243] The highly stabilized formulations of the present disclosure include furin, *e.g.*, rfurin, and one or more of stabilizing agents, buffering agents, sodium chloride, salts, and other excipients. Such components are described in further detail below. As will be appreciated, any of the formulation components described herein can be used singly or in any combination.

[0244] The highly stabilized Furin formulations of the present disclosure show increased stability toward shear (agitation), lyophilization, and freeze/thaw stress as well as resistance to product loss or denaturation at container surfaces as compared to control or starting formulations.

[0245] Furin is included in formulations of the present disclosure in concentrations from 5,000 to 500,000 U/mL. In certain embodiments, Furin is included in concentrations from 5,500 to 55,000, from 6,000 to 50,000, from 6,500 to 45,000, from 7,000 to 40,000, from 7,500 to 35,000, from 8,000 to 30,000, from 8,500 to 25,000, from 9,000 to 20,000, from 9,500 to 15,000, and about 10,000 U/mL. In yet other embodiments, furin is included in the formulations of the present disclosure at a concentration selected from variations 6470 to 6533 found in Table 14, reported in thousands of Units of furin activity per mL. In specific embodiments, the furin contained in the highly stabilized formulations of the present disclosure is rfurin.

Table 14. Exemplary furin (*e.g.*, rfurin) concentrations (expressed in thousands of Units furin activity per mL) used in the stabilized compositions provided herein.

1-1,000	Var. 6470	5-450	Var. 6492	8-150	Var. 6514
1-900	Var. 6471	5-400	Var. 6493	8-100	Var. 6515
1-800	Var. 6472	5-350	Var. 6494	8-52	Var. 6516
1-700	Var. 6473	5-300	Var. 6495	8-50	Var. 6517
1-600	Var. 6474	5-250	Var. 6496	10-1,000	Var. 6518
1-500	Var. 6475	5-200	Var. 6497	10-900	Var. 6519
1-450	Var. 6476	5-150	Var. 6498	10-800	Var. 6520
1-400	Var. 6477	5-100	Var. 6499	10-700	Var. 6521
1-350	Var. 6478	5-52	Var. 6500	10-600	Var. 6522
1-300	Var. 6479	5-50	Var. 6501	10-500	Var. 6523
1-250	Var. 6480	8-1,000	Var. 6502	10-450	Var. 6524
1-200	Var. 6481	8-900	Var. 6503	10-400	Var. 6525
1-150	Var. 6482	8-800	Var. 6504	10-350	Var. 6526
1-100	Var. 6483	8-700	Var. 6505	10-300	Var. 6527
1-52	Var. 6484	8-600	Var. 6506	10-250	Var. 6528
1-50	Var. 6485	8-500	Var. 6507	10-200	Var. 6529

5-1,000	Var. 6486	8-450	Var. 6508	10-150	Var. 6530
5-900	Var. 6487	8-400	Var. 6509	10-100	Var. 6531
5-800	Var. 6488	8-350	Var. 6510	10-52	Var. 6532
5-700	Var. 6489	8-300	Var. 6511	10-50	Var. 6533
5-600	Var. 6490	8-250	Var. 6512		
5-500	Var. 6491	8-200	Var. 6513		

Var. = Variation

[0246] In another embodiment, the furin (*e.g.*, rfurin) concentration of a stabilized composition provided herein can be expressed as the mass of furin present in the composition. In one embodiment, furin (*e.g.*, rfurin) is present in a stabilized composition as described herein at a concentration from 100 ng/mL to 100 mg/mL. In another embodiment, furin (*e.g.*, rfurin) is present in a stabilized composition as described herein at a concentration from 1 μg/mL to 10 mg/mL. In another embodiment, furin (*e.g.*, rfurin) is present in a stabilized composition as described herein at a concentration from 1 μg/mL to 1 mg/mL. In yet other embodiments, furin (*e.g.*, rfurin) is present in a stabilized composition as described herein at a concentration selected from variations 6534 to 6638 found in Table 15. In specific embodiments, the furin contained in the highly stabilized formulations of the present disclosure is rfurin.

Table 15. Exemplary furin (*e.g.*, rfurin) concentrations used in the stabilized compositions provided herein.

100 ng/mL to 100 mg/mL	Var. 6534	25 μg/mL to 10 mg/mL	Var. 6587
100 ng/mL to 50 mg/mL	Var. 6535	25 μg/mL to 5 mg/mL	Var. 6588
100 ng/mL to 25 mg/mL	Var. 6536	25 μg/mL to 1 mg/mL	Var. 6589
100 ng/mL to 10 mg/mL	Var. 6537	25 μg/mL to 500 μg/mL	Var. 6590
100 ng/mL to 5 mg/mL	Var. 6538	25 μg/mL to 250 μg/mL	Var. 6591
100 ng/mL to 1 mg/mL	Var. 6539	25 μg/mL to 100 μg/mL	Var. 6592
100 ng/mL to 500 μg/mL	Var. 6540	25 μg/mL to 50 μg/mL	Var. 6593
100 ng/mL to 250 μg/mL	Var. 6541	50 μg/mL to 100 mg/mL	Var. 6594
100 ng/mL to 100 μg/mL	Var. 6542	50 μg/mL to 50 mg/mL	Var. 6595
100 ng/mL to 50 μg/mL	Var. 6543	50 μg/mL to 25 mg/mL	Var. 6596
100 ng/mL to 25 μg/mL	Var. 6544	50 μg/mL to 10 mg/mL	Var. 6597
100 ng/mL to 10 μg/mL	Var. 6545	50 μg/mL to 5 mg/mL	Var. 6598
100 ng/mL to 5 μg/mL	Var. 6546	50 μg/mL to 1 mg/mL	Var. 6599
100 ng/mL to 1 μg/mL	Var. 6547	50 μg/mL to 500 μg/mL	Var. 6600
1 μg/mL to 100 mg/mL	Var. 6548	50 μg/mL to 250 μg/mL	Var. 6601
1 μg/mL to 50 mg/mL	Var. 6549	50 μg/mL to 100 μg/mL	Var. 6602
1 μg/mL to 25 mg/mL	Var. 6550	100 μg/mL to 100 mg/mL	Var. 6603
1 μg/mL to 10 mg/mL	Var. 6551	100 μg/mL to 50 mg/mL	Var. 6604
1 μg/mL to 5 mg/mL	Var. 6552	100 μg/mL to 25 mg/mL	Var. 6605

1 µg/mL to 1 mg/mL	Var. 6553	100 µg/mL to 10 mg/mL	Var. 6606
1 µg/mL to 500 µg/mL	Var. 6554	100 µg/mL to 5 mg/mL	Var. 6607
1 µg/mL to 250 µg/mL	Var. 6555	100 µg/mL to 1 mg/mL	Var. 6608
1 µg/mL to 100 µg/mL	Var. 6556	100 µg/mL to 500 µg/mL	Var. 6609
1 µg/mL to 50 µg/mL	Var. 6557	100 µg/mL to 250 µg/mL	Var. 6610
1 µg/mL to 25 µg/mL	Var. 6558	250 µg/mL to 100 mg/mL	Var. 6611
1 µg/mL to 10 µg/mL	Var. 6559	250 µg/mL to 50 mg/mL	Var. 6612
1 µg/mL to 5 µg/mL	Var. 6560	250 µg/mL to 25 mg/mL	Var. 6613
5 µg/mL to 100 mg/mL	Var. 6561	250 µg/mL to 10 mg/mL	Var. 6614
5 µg/mL to 50 mg/mL	Var. 6562	250 µg/mL to 5 mg/mL	Var. 6615
5 µg/mL to 25 mg/mL	Var. 6563	250 µg/mL to 1 mg/mL	Var. 6616
5 µg/mL to 10 mg/mL	Var. 6564	250 µg/mL to 500 µg/mL	Var. 6617
5 µg/mL to 5 mg/mL	Var. 6565	500 µg/mL to 100 mg/mL	Var. 6618
5 µg/mL to 1 mg/mL	Var. 6566	500 µg/mL to 50 mg/mL	Var. 6619
5 µg/mL to 500 µg/mL	Var. 6567	500 µg/mL to 25 mg/mL	Var. 6620
5 µg/mL to 250 µg/mL	Var. 6568	500 µg/mL to 10 mg/mL	Var. 6621
5 µg/mL to 100 µg/mL	Var. 6569	500 µg/mL to 5 mg/mL	Var. 6622
5 µg/mL to 50 µg/mL	Var. 6570	500 µg/mL to 1 mg/mL	Var. 6623
5 µg/mL to 25 µg/mL	Var. 6571	1 mg/mL to 100 mg/mL	Var. 6624
5 µg/mL to 10 µg/mL	Var. 6572	1 mg/mL to 50 mg/mL	Var. 6625
10 µg/mL to 100 mg/mL	Var. 6573	1 mg/mL to 25 mg/mL	Var. 6626
10 µg/mL to 50 mg/mL	Var. 6574	1 mg/mL to 10 mg/mL	Var. 6627
10 µg/mL to 25 mg/mL	Var. 6575	1 mg/mL to 5 mg/mL	Var. 6628
10 µg/mL to 10 mg/mL	Var. 6576	5 mg/mL to 100 mg/mL	Var. 6629
10 µg/mL to 5 mg/mL	Var. 6577	5 mg/mL to 50 mg/mL	Var. 6630
10 µg/mL to 1 mg/mL	Var. 6578	5 mg/mL to 25 mg/mL	Var. 6631
10 µg/mL to 500 µg/mL	Var. 6579	5 mg/mL to 10 mg/mL	Var. 6632
10 µg/mL to 250 µg/mL	Var. 6580	10 mg/mL to 100 mg/mL	Var. 6633
10 µg/mL to 100 µg/mL	Var. 6581	10 mg/mL to 50 mg/mL	Var. 6634
10 µg/mL to 50 µg/mL	Var. 6582	10 mg/mL to 25 mg/mL	Var. 6635
10 µg/mL to 25 µg/mL	Var. 6583	25 mg/mL to 100 mg/mL	Var. 6636
25 µg/mL to 100 mg/mL	Var. 6584	25 mg/mL to 50 mg/mL	Var. 6637
25 µg/mL to 50 mg/mL	Var. 6585	50 mg/mL to 100 mg/mL	Var. 6638
25 µg/mL to 25 mg/mL	Var. 6586		

Var. = Variation

[0247] In some aspects of the present disclosure, furin (*e.g.*, rfurin) formulations include calcium or another divalent metal cations. In further aspects, the divalent cation is present as a salt, preferably a chloride salt. In certain embodiments, from 0.1 mM to 10 mM of a divalent cation salt can be used, or from 0.5 mM to 2 mM, or about 0.92 mM. In still further embodiments, from 0.5 mM to 9 mM, from 1 mM to 8 mM, from 1.5 mM to 7 mM, from 2 mM to 6 mM, from 2.5 mM to 5 mM, or from 3 mM to 4.5 mM divalent cation salt is used in

formulations of the invention. When calcium salt is used, it is preferably calcium chloride, but can also be other calcium salts such as calcium gluconate, calcium glubionate, or calcium gluceptate. Divalent cations, including calcium, can be included in combination with one or more other formulation components disclosed herein. Non-limiting examples of divalent metal cations useful in the formulations provided herein include calcium, barium, manganese, magnesium, cobalt, copper, nickel, and zinc.

[0248] In some embodiments, the furin (*e.g.*, rfurin) formulations include an antioxidant. The addition of antioxidants to aqueous and lyophilized formulations has been found to improve the stability of these formulations, and thus extend their shelf lives. The antioxidants used must be compatible for use with a pharmaceutical preparation, and in addition are preferably water soluble. When adding antioxidants to a formulation, it is preferable to add such antioxidants as late in the process prior to lyophilization as possible, in order to avoid spontaneous oxidation of the antioxidant. Table 2 below lists suitable antioxidants, which are available commercially through companies such as Calbiochem and Sigma.

Table 16. Exemplary Antioxidants

N-Acetyl-L-Cysteine / Homocysteine
Glutathione
6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox)
Lipoic acid
Methionine
Sodium Thiosulfate
Platinum
Glycme-glycine-histidme (tripeptide)
Butylatedhydroxytoluene (BHT)

[0249] Concentrations in the range of about 0.05 mg/ml to more than 1.0 mg/ml of antioxidants can be used, and it is believed that higher concentrations would also be useful (up to the point of any toxic effects or adverse manufacturing effects, such as a depression of the glass transition temperature of the lyophilized product). Accordingly, in one embodiment, the furin (*e.g.*, rfurin) composition comprises from 0.05 mg/mL to 1.0 mg/mL antioxidant. In other embodiments, the furin (*e.g.*, rfurin) composition comprises from 0.05 to 0.5 mg/mL, 0.1 mg/mL to 0.9 mg/mL, 0.1 mg/mL to 0.8 mg/mL, 0.1 mg/mL to 0.7 mg/mL, 0.1 mg/mL to 0.6 mg/mL,

0.1 mg/mL to 0.5 mg/mL, 0.1 mg/mL to 0.4 mg/mL, 0.1 mg/mL to 0.3 mg/mL, 0.1 mg/mL to 0.2 mg/mL, 0.2 mg/mL to 0.9 mg/mL, 0.2 mg/mL to 0.8 mg/mL, 0.2 mg/mL to 0.7 mg/mL, 0.2 mg/mL to 0.6 mg/mL, 0.2 mg/mL to 0.5 mg/mL, 0.2 mg/mL to 0.4 mg/mL, 0.2 mg/mL to 0.3 mg/mL, 0.3 mg/mL to 0.7 mg/mL, 0.4 mg/mL to 0.6 mg/mL antioxidant.

E. Formulation Development

[0250] In certain aspects of the present disclosure, highly stabilized formulations of furin (*e.g.*, rfurin) are prepared by providing a starting (control) furin formulation and adding components to achieve a desired level of component concentrations. For example, the addition of one part 750 ppm non-ionic surfactant to 9 parts furin composition lacking non-ionic surfactant to provide a final formulation comprising 75 ppm non-ionic surfactant. This process is also called "spiking in" to a starting formulation.

[0251] In certain embodiments, to produce the highly stabilized furin (*e.g.*, rfurin) formulations of the present disclosure, furin is contained in a starting formulation and a buffer composition is spiked into the starting formulation. In other embodiments, the highly stabilized furin (*e.g.*, rfurin) formulation is formed using dialysis according to methods known in the art. In some embodiments, the methods of formulation involve spiking a concentrated buffer composition into a starting formulation of furin. In one embodiment, polysorbate 80 is added to the starting formulation prior to the addition of other components, particularly prior to the addition of trehalose, in order to protect Furin against agitation during mixing.

[0252] In an exemplary embodiment, furin (*e.g.*, rfurin) bulk drug substance (BDS) is contained in a starting formulation of 10 mM sodium acetate, 230 mM sodium chloride, 1 mM calcium chloride, pH 6.0. In one embodiment, the following components are spiked into the starting formulation: 1% polysorbate 80, 500 mM HEPES, 400 mM acetic acid, 1 mM CaCl2, pH 6.0 and trehalose dihydrate powder to attain the following composition: 46 mM HEPES, 45 mM acetic acid, 190 mM NaCl, 0.92 mM CaCl2, 75 ppm polysorbate 80, 10% w/w trehalose dihydrate, pH 6.0. The increase in acetic acid and the addition of HEPES results in greater stability of the pH. Although at pH 6.0 both acetic acid and HEPES are outside of their highest buffering capacity, the high concentration of these chemicals greatly increases the buffering capacity of the highly stabilized formulation. In certain embodiments, the polysorbate 80 is

added to the starting formulation prior to the other components to protect furin from aggregation and adsorption to container surfaces during mixing when the other reagents are added. In certain embodiments, the furin in the starting formulation is mixed with polysorbate 80 and/or any other components except for trehalose. Trehalose and any remaining components are added after polysorbate 80 is added to protect furin from aggregation and adsorption during mixing.

[0253] In certain embodiments, the stabilized formulation is combined with a diluent so that the formulation can be used in methods such as an rVWF maturation process. In further embodiments, a stabilized diluent is prepared by spiking a starting diluent (50 mM HEPES, 150 mM NaCl, 1 mM CaCl2, pH 7.0) with polysorbate 80 to 75 ppm. The combination of the highly stabilized furin (*e.g.*, rfurin) formulation of the present disclosure with this stabilized diluent increases furin recovery in the rVWF maturation step by three to four times compared to the use of the starting furin and diluent formulations.

[0254] In certain embodiments, the highly stabilized furin formulations of the present disclosure are lyophilized. During lyophilization, the formulation is converted from being in an aqueous phase to being in an amorphous solid phase, which is thought to protect the protein from chemical and/or conformational instability. In further embodiments, the lyophilized preparation not only contains an amorphous phase, but also includes a component which crystallizes during lyophilization.

[0255] One or more components of highly stabilized formulations may in some embodiments be dispersed in the amorphous phase of the lyophilized cake. In addition, the apparent glass transition temperature (Tg') of the amorphous phase is preferably relatively high during freeze-drying, and the glass transition temperature (Tg) of the solid is likewise preferably high during storage.

IV. Methods for Diluting Aqueous Compositions of Recombinant furin

[0256] In one aspect, the present disclosure provides methods for diluting aqueous compositions of furin (*e.g.*, rfurin). The following embodiments are based in part on the discovery that inclusion of a non-ionic surfactant in a buffer used to dilute furin (*e.g.*, rfurin) results in the recovery of 3-4 times more furin activity as compared to dilution with a buffer lacking the non-ionic surfactant.

[0257] In one embodiment, the method includes adding a dilution buffer containing non-ionic surfactant to a furin (*e.g.*, rfurin) composition, to form a diluted furin (*e.g.*, rfurin) composition. In some embodiments, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 1,000:1 (dilution buffer:furin composition). In another embodiment, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 500:1 (dilution buffer:furin composition). In another embodiment, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 250:1 (dilution buffer:furin composition). In another embodiment, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 200:1 (dilution buffer:furin composition). In another embodiment, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 100:1 (dilution buffer:furin composition). In another embodiment, the dilution buffer is added at a ratio of from 1:1 (dilution buffer:furin composition) to 50:1 (dilution buffer:furin composition).

[0258] In one embodiment, the method comprises a first step of adding a non-ionic surfactant to a furin (*e.g.*, rfurin) composition and a second step of adding a dilution buffer to the furin (*e.g.*, rfurin) composition containing the non-ionic surfactant, to form a diluted furin composition. In one embodiment, the surfactant will be added to the furin composition at a final concentration of X-fold a desired concentration in the diluted furin composition, where X is the dilution factor. For example, if a final concentration of 10 ppm non-ionic surfactant is desired in a furin composition to be diluted 100-fold, the non-ionic surfactant is added to the starting furin composition at a final concentration of 1,000 ppm (10 ppm x 100-fold dilution), and the composition is subsequently diluted by adding 99 parts dilution buffer per 1 part starting solution (accounting for volume added during addition of the non-ionic surfactant).

[0259] In certain embodiments, the furin (*e.g.*, rfurin) composition is diluted from 1-fold to 1,000-fold, from 1-fold to 500-fold, from 1-fold to 250-fold, from 1-fold to 200-fold, from 1-fold to 100-fold, from 1-fold to 50-fold, from 1-fold to 10-fold, from 10-fold to 1,000-fold, from 10-fold to 500-fold, from 10-fold to 250-fold, from 10-fold to 200-fold, from 10-fold to 100-fold, from 10-fold to 50-fold, from 50-fold to 1,000-fold, from 50-fold to 500-fold, from 50-fold to 250-fold, from 50-fold to 200-fold, from 50-fold to 100-fold, from 100-fold to 1,000-fold, from 100-fold to 500-fold, from 100-fold to 250-fold, from 100-fold to 200-fold, from 200-fold to 1,000-fold, from 200-fold to 500-fold, or from 200-fold to 250-fold.

A. Furin Dilution Buffer

[0260] In one embodiment, the furin dilution buffer will include a pharmaceutically acceptable salt, non-ionic surfactant, and a buffering agent. In one embodiment, the dilution buffer further includes calcium. In another embodiment, the dilution buffer further includes a sugar and/or sugar alcohol.

[0261] In one embodiment, pharmaceutically acceptable salt is present in the dilution buffer at a concentration of from 10 mM to 500 mM. In another embodiment, the concentration of pharmaceutically acceptable salt is from 100 mM to 300 mM. In another embodiment, the concentration of pharmaceutically acceptable salt is from 150 mM to 250 mM. In yet other embodiments, the concentration of pharmaceutically acceptable salt in the furin dilution buffer is selected from variations 6036 to 6180 found in Table 10. In one embodiment, the pharmaceutically acceptable salt is sodium chloride, potassium chloride, or a combination thereof. In a specific embodiment, pharmaceutically acceptable salt is sodium chloride. In another specific embodiment, pharmaceutically acceptable salt is potassium chloride.

[0262] In one embodiment, the dilution buffer has a pH of from 5.5 to 7.5. In one embodiment, the pH of the dilution buffer is from 5.5 to 7.0. In another embodiment, the pH of the dilution buffer is from 5.5 to 6.5. In another embodiment, the pH of the dilution buffer is 6.0±0.2. In a specific embodiment, the pH of the dilution buffer is 6.0. In other embodiments, the dilution buffer has a pH selected from variations 6181 to 6403 found in Table 11.

[0263] In one embodiment, buffering agent is present in the dilution buffer at a concentration of from 10 mM to 300 mM. In another embodiment, the concentration of buffering agent in the dilution buffer is between 10 mM to 200 mM. In other embodiments, the concentration of buffering agent in the dilution buffer is selected from variations 6404 to 6469 found in Table 12. In one embodiment, the buffering agent is acetate, HEPES, or a combination thereof. In a specific embodiment, the buffering agent is a combination of acetate and HEPES.

[0264] In some embodiments, the furin dilution buffer includes calcium or another divalent metal cation. In one embodiment, the divalent cation is added as a salt, preferably a chloride salt. In certain embodiments, the concentration of divalent cation (*e.g.*, calcium) in the dilution buffer is from 0.1 mM to 10 mM, from 0.5 mM to 2 mM, or about 0.92 mM. In still further

embodiments, from 0.5 mM to 9 mM, from 1 mM to 8 mM, from 1.5 mM to 7 mM, from 2 mM to 6 mM, from 2.5 mM to 5 mM, or from 3 mM to 4.5 mM divalent cation is used in the dilution buffer. When calcium salt is used, it is preferably calcium chloride, but can also be other calcium salts such as calcium gluconate, calcium glubionate, or calcium gluceptate. Divalent cations, including calcium, can be included in combination with one or more other formulation components disclosed herein. Non-limiting examples of divalent metal cations useful in the dilution buffers provided herein include calcium, barium, manganese, magnesium, cobalt, copper, nickel, and zinc.

[0265] In some embodiments, the furin dilution buffer includes a sugar and/or sugar alcohol. In one embodiment, the dilution buffer contains a monosaccharide sugar. In a particular embodiment, the monosaccharide sugar is selected from the group consisting of a diose sugar, a triose sugar, a tetrose sugar, a pentose sugar, a hexose sugar, a heptose sugar, and an octose sugar. In a particular embodiment, the sugar is a pentose sugar, a hexose sugar, or a combination thereof. In a specific embodiment, the sugar is a hexose sugar.

[0266] In another embodiment, the dilution buffer contains a disaccharide sugar. In a particular embodiment, the disaccharide sugar is selected from disaccharide sugars formed from pentose and/or hexose monosaccharides. In another particular embodiment, the sugar is selected from disaccharide sugars formed from hexose monosaccharides. In one embodiment, the sugar is sucrose, trehalose, or a combination thereof. In one specific embodiment, the sugar is sucrose. In another specific embodiment, the sugar is trehalose. In one embodiment, the sugar is formulated as trehalose dihydrate.

[0267] In another embodiment, the dilution buffer contains a sugar alcohol. In a particular embodiment, the sugar alcohol is selected from glycol, glycerol, erythritol, threitol, ribitol, fucitol, iditol, volmitol, isomalt, maltitol, lactitol, mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol. In another particular embodiment, the sugar alcohol is mannitol.

[0268] In yet another embodiment, the dilution buffer contains a mixture of sugar and sugar alcohol. In one embodiment, the mixture contains at least two of a monosaccharide, a disaccharide, and a sugar alcohol. In another embodiment, the mixture contains at least two of a pentose sugar, a hexose sugar, a disaccharide formed from pentose and/or hexose

monosaccharides, and a sugar alcohol. In another embodiment, the mixture contains at least two of sucrose, trehalose, and mannitol.

[0269] In one embodiment, the sugar or sugar alcohol is present in the dilution buffer at a concentration of from 2% to 20%, 2% to 17.5%, 2% to 15%, 2% to 12.5%, 2% to 10%, 2% to 9%, 2% to 8%, 2% to 7%, 5% to 20%, 5% to 17.5%, 5% to 15%, 5% to 12.5%, 5% to 10%, 7.5% to 20%, 7.5% to 17.5%, 7.5% to 15%, 7.5% to 12.5%, 10% to 20%, 10% to 17.5%, 10% to 15%, 4±2%, 5±2%, 6±2%, 7±2%, 8±2%, 9±2%, 10±2%, 11±2%, 12±2%, 13±2%, 14±2%, 15±2%, 16±2%, 17±2%, 18±2%, 3±1%, 4±1%, 5±1%, 6±1%, 7±1%, 8±1%, 9±1%, 10±1%, 11±1%, 12±1%, 13±1%, 14±1%, 15±1%, 16±1%, 17±1%, 18±1%, 19±1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20%. In one embodiment, the sugar or sugar alcohol is selected from sucrose, trehalose, mannitol, and a combination thereof. In a specific embodiment, the sugar or sugar alcohol is trehalose.

[0270] In one embodiment, storage stable compositions of furin (*e.g.*, rfurin) are provided which contain a non-ionic surfactant selected from a non-ionic water soluble monoglyceride, a non-ionic water soluble diglyceride, a non-ionic water soluble triglyceride, a non-ionic water soluble monofatty acid esters of polyethyelene glycol, a non-ionic water soluble difatty acid esters of polyethyelene glycol, a non-ionic water soluble sorbitan fatty acid ester, a non-ionic polyglycolyzed glyceride, a non-ionic water soluble triblock copolymer, and a combination thereof. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

1. Non-Ionic Surfactants

[0271] In one embodiment, the furin dilution buffer, or non-ionic surfactant solution added prior to dilution, contains a non-ionic surfactant selected from a non-ionic water soluble monoglyceride, a non-ionic water soluble diglyceride, a non-ionic water soluble triglyceride, a non-ionic water soluble monofatty acid esters of polyethyelene glycol, a non-ionic water soluble difatty acid esters of polyethyelene glycol, a non-ionic water soluble sorbitan fatty acid ester, a non-ionic polyglycolyzed glyceride, a non-ionic water soluble triblock copolymer, and a combination thereof. In one embodiment, the non-ionic surfactant is a non-ionic water soluble

sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0272] In one embodiment, the non-ionic surfactant is present in the dilution buffer at a concentration of from 10 to 200 ppm, 10 to 175 ppm, 10 to 150 ppm, 10 to 125 ppm, 10 to 100 ppm, 10 to 90 ppm, 10 to 80 ppm, 10 to 75 ppm, 10 to 70 ppm, 10 to 60 ppm, 10 to 50 ppm, 10 to 25 ppm, 25 to 200 ppm, 25 to 175 ppm, 25 to 150 ppm, 25 to 125 ppm, 25 to 100 ppm, 25 to 90 ppm, 25 to 80 ppm, 25 to 70 ppm, 25 to 60 ppm, 25 to 50 ppm, 50 to 200 ppm, 50 to 175 ppm, 50 to 150 ppm, 50 to 125 ppm, 50 to 90 ppm, 50 to 80 ppm, 75 to 200 ppm, 75 to 175 ppm, 75 to 150 ppm, 100 to 200 ppm, 100 to 175 ppm, 50±25 ppm, 60±25 ppm, 70±25 ppm, 75±25 ppm, 80±25 ppm, 90±25 ppm, 100±25 ppm, 125±25 ppm, 150±25 ppm, 175±25 ppm, 30±10 ppm, 40±10 ppm, 50±10 ppm, 60±10 ppm, 70±10 ppm, 75±10 ppm, 80±10 ppm, 90±10 ppm, 100±10 ppm, 110±10 ppm, 120±10 ppm, 125±10 ppm, 130±10 ppm, 140±10 ppm, 150±10 ppm, 160±10 ppm, 170±10 ppm, 175±10 ppm, 180±10 ppm, 190±10 ppm, 25 ppm, 30 ppm, 40 ppm, 50 ppm, 60 ppm, 70 ppm, 75 ppm, 80 ppm, 90 ppm, 100 ppm, 110 ppm, 120 ppm, 125 ppm, 130 ppm, 140 ppm, 150 ppm, 160 ppm, 170 ppm, 175 ppm, 180 ppm, 190 ppm, or 200 ppm. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0273] In one embodiment, the target concentration of non-ionic surfactant after dilution is from 10 to 200 ppm, 10 to 175 ppm, 10 to 150 ppm, 10 to 125 ppm, 10 to 100 ppm, 10 to 90 ppm, 10 to 80 ppm, 10 to 75 ppm, 10 to 70 ppm, 10 to 60 ppm, 10 to 50 ppm, 10 to 25 ppm, 25 to 200 ppm, 25 to 175 ppm, 25 to 150 ppm, 25 to 125 ppm, 25 to 100 ppm, 25 to 90 ppm, 25 to 80 ppm, 25 to 70 ppm, 25 to 60 ppm, 25 to 50 ppm, 50 to 200 ppm, 50 to 175 ppm, 50 to 150 ppm, 50 to 125 ppm, 50 to 90 ppm, 50 to 80 ppm, 75 to 200 ppm, 75 to 175 ppm, 75 to 150 ppm, 100 to 200 ppm, 100 to 175 ppm, 50±25 ppm, 60±25 ppm, 70±25 ppm, 75±25 ppm, 80±25 ppm, 90±25 ppm, 100±25 ppm, 125±25 ppm, 150±25 ppm, 175±25 ppm, 30±10 ppm, 40±10 ppm, 50±10 ppm, 60±10 ppm, 70±10 ppm, 75±10 ppm, 80±10 ppm, 90±10 ppm, 100±10 ppm, 110±10 ppm, 120±10 ppm, 125±10 ppm, 130±10 ppm, 140±10 ppm, 150±10 ppm, 160±10 ppm, 170±10 ppm, 175±10 ppm, 180±10 ppm, 190±10 ppm, 25 ppm, 30 ppm, 40 ppm, 50 ppm, 60 ppm, 70 ppm, 75 ppm, 80 ppm, 90 ppm, 100 ppm, 110 ppm, 120 ppm, 125 ppm, 130 ppm, 140

ppm, 150 ppm, 160 ppm, 170 ppm, 175 ppm, 180 ppm, 190 ppm, or 200 ppm. In one embodiment, the non-ionic surfactant is a non-ionic water soluble sorbitan fatty acid ester. In a specific embodiment, the non-ionic surfactant is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0274] In one embodiment, the inclusion of a non-ionic surfactant in a furin dilution buffer, or addition prior to dilution, increases the furin activity recovered in a diluted furin composition by at least 10%, as compared to the activity recovered in a furin composition diluted without use of the non-ionic surfactant, or with the use of the non-ionic surfactant at a lower concentration. In other embodiments, the furin activity recovered after dilution using a non-ionic surfactant is at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 2-fold, 3-fold, 4-fold, 5-fold, or more greater than the furin activity recovered after dilution without the non-ionic surfactant, or using a lower concentration of the non-ionic surfactant.

V. Stability Assays

[0275] As discussed herein, the highly stabilized furin (*e.g.*, rfurin) formulations of the present disclosure show improved stability as compared to control formulations. In one embodiment, improved stability includes retention of a higher percentage of activity than control formulations in various stability assays. Such assays can be used to determine if a formulation is a highly stabilized formulation. In some embodiments, the highly stabilized formulation has at least 5%, 10%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or greater activity than a control formulation when assessed by any of the stability assays discussed herein or known in the art.

[0276] In further aspects, furin (*e.g.*, rfurin) formulations are tested under stressor conditions, such as storage at high temperature, agitation, freeze/thaw cycles, or some combination thereof. After such stressors, the formulations are assayed using any of the methods described herein or known in the art to determine the stability under these conditions.

[0277] In one aspect, furin activity assays are used to assess the stability of a formulation. In some embodiments, a furin activity assays involve a measurement of substrate cleavage. In one embodiment, the substrate is Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1; AMC =

7-amino-4-methoxy coumarin), which is cleaved by furin, liberating 7-amino-4-methoxy coumarin. The assay is performed, for example, on an ELISA plate. The furin activity in a sample is determined from a standard curve created, for example, from a quality control (QC) furin standard. The activity values are generally calculated as mean values from two dilutions, each in duplicate.

[0278] In another aspect, size exclusion chromatography (SEC) is used to evaluate the stability of a furin (*e.g.*, rfurin) formulation. In such assays, stability is indicated by the height of the peak corresponding to monomeric furin. A reduction in monomer peak height means the product is being lost (unstable) and the generation of higher molecular weight peaks indicates that aggregation is occurring and lower molecular weight peaks means the product is degrading. In an exemplary embodiment, after 4 days at 37°C, the relative peak height of a control furin formulation was 58.5%, but in a highly stabilized formulation, the relative peak height was 74.8% (FIG. 48). Thus, the highly stabilized formulation maintained the stability of furin in the composition and retained a larger percentage of the peak height as compared to that seen prior to storage at four days at a higher (37°C) temperature.

[0279] In another aspect, qualitative assays such as Western Blot analyses, are used to evaluate the stability of a Furin formulation. For example, Figure 26 shows that after 5 days at 35°C, a greater percent of the signal is present as the intact furin molecule rather than the degraded species in the stabilized formulation (lane 11), as compared to a non-stabilized formulation (lane 5).

[0280] In still another aspect, qualitative assays such as UV spectra are used to evaluate stability. Such assays are particularly useful when the stressor used is agitation. The UV spectra can indicate the presence of aggregate – the presence of an aggregate is an indication of instability. For example, Figure 36 shows a major displacement of the spectra upward (indicating aggregation) when the control formulation is agitated. Figures 41 and 42 show the protective power of a highly stabilized formulation in that, with agitation, the spectra of the agitated sample is not displaced upward, but overlays the non-agitated sample, which indicates that aggregation was not formed when the formulation was placed under stress through agitation.

[0281] The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the example herein below. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as Genome Analysis: A Laboratory Manual Series (Vols. I-IV), Using Antibodies: A Laboratory Manual, Cells: A Laboratory Manual, PCR Primer: A Laboratory Manual, and Molecular Cloning: A Laboratory Manual (all from Cold Spring Harbor Laboratory Press), Stryer, L. (1995) Biochemistry (4th Ed.) Freeman, Highly stabilized York, Gait, "Oligonucleotide Synthesis: A Practical Approach" 1984, IRL Press, London, Nelson and Cox (2000), Lehninger, Principles of Biochemistry 3rd Ed., W. H. Freeman Pub., Highly stabilized York, N.Y. and Berg et al. (2002) Biochemistry, 5th Ed., W. H. Freeman Pub., Highly stabilized York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

[0282] In the following description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

[0283] Although the present invention is described primarily with reference to specific embodiments, it is also envisioned that other embodiments will become apparent to those skilled in the art upon reading the present disclosure, and it is intended that such embodiments be contained within the present inventive methods.

EXAMPLES

Example 1 – Storage stability of aqueous rfurin formulations

[0284] The stability of a control furin formulation was tested at three different temperatures: room temperature (*e.g.*, 25°C), 37°C, and 45°C. These studies at elevated temperatures were used to study accelerated stability, which is comparable to long term studies of stability at lower temperatures. The samples were tested at time zero, then after 1, 2, 3, 4, and 7 days of incubation. Analyses included the furin activity assay, SEC, and western blotting.

[0285] Briefly, several 5 mL polypropylene vials were filled with 3 mL of rfurin and incubated at three different temperatures: ambient (room), 37°C and 45°C. One vial from each incubation condition was taken out at time zero, then after 1, 2, 3, 4, and 7 days. 200 µL aliquots were made into 0.65 mL polypropylene vials and frozen at -80°C awaiting analyses.

[0286] The stability of several furin formulations was determined under these conditions. Specifics of the various formulations are given in Table 17.

Table 17. Furin formulations tested for stability during storage at elevated temperatures.

Control Formulation	10 mM Acetate 230 mM sodium chloride 1 mM calcium chloride pH 6.0
Test Formulation #1	46 mM HEPES 45 mM Acetate 190 mM sodium chloride 0.92 mM calcium chloride 75 ppm polysorbate 80 10% (w/w) trehalose dehydrate pH 6.0
Test Formulation #2	46 mM HEPES 45 mM Acetate 190 mM sodium chloride 0.92 mM calcium chloride 10% (w/w) trehalose dehydrate pH 6.0
Test Formulation #3	46 mM HEPES 45 mM Acetate

	190 mM sodium chloride 0.92 mM calcium chloride 10 ppm polysorbate 80 10% (w/w) trehalose dehydrate pH 6.0
Test Formulation #4	46 mM HEPES 45 mM Acetate 190 mM sodium chloride 0.92 mM calcium chloride 25 ppm polysorbate 80 10% (w/w) trehalose dehydrate pH 6.0
Test Formulation #5	46 mM HEPES 45 mM Acetate 190 mM sodium chloride 0.92 mM calcium chloride 50 ppm polysorbate 80 10% (w/w) trehalose dehydrate pH 6.0
Test Formulation #6	46 mM HEPES 45 mM Acetate 190 mM sodium chloride 0.92 mM calcium chloride 100 ppm polysorbate 80 10% (w/w) trehalose dehydrate pH 6.0

[0287] One method of assessing stability is through a furin activity assay. In this assay, the activity of furin is determined from the rate of a substrate cleavage. The substrate, Boc-Arg-Val-Arg-Arg-AMC (SEQ ID NO:1; AMC = 7-amino-4-methoxy coumarin), is cleaved by furin and a fluorescent AMC is liberated. The assay is performed, for example, on an ELISA plate. The furin activity in a sample is determined from a standard curve created, for example, from a quality control rfurin standard. The activity values were calculated as mean values from two dilutions, each in duplicate.

[0288] rFurin stability at 37°C in the highly stabilized formulation. The purpose of this experiment was to test rfurin stability in a stabilized formulation containing 75 ppm polysorbate

80. There was a small change in the composition of this sample because trehalose dihydrate ($C_{12}H_{22}O_{11}$*$2H_2O$, FW 378.33) was used, rather than, nonhydrated trehalose ($C_{12}H_{22}O_{11}$, FW 342.30). Use of the trehalose dihydrate created a slightly more dilute sample. Agitation studies suggested that the polysorbate 80 concentration should be kept between 50 ppm and 100 ppm to provide the best protection against rfurin denaturation induced by agitation. In this study, a rfurin sample in test formulation #1 was spiked with polysorbate 80 to 75 ppm and incubated at 37°C for four days. An rfurin sample formulated with the control formulation served as a control.

[0289] Analyses by the Furin activity assay (Figure 1) show loss of activity in the samples in the control formulation that were incubated at 37°C and 45°C. Since the 45°C sample was highly degraded and aggregated after just two days, the sample was not tested after that time. For the samples incubated at room temperature, the data was inconclusive as a result of the amount of variability in the assay, but the data suggested that the rfurin activity was relatively stable, with the activity after 7 days roughly equivalent to T=0.

[0290] In contrast to the data in the control formulation, analyses by the furin activity assay (Figure 46) show that rfurin in test formulation #1 retained more of its activity than in the control formulation. After four days of incubation at 37°C, rfurin retained 76.7% of its original activity, while the control formulation preserved only 55.5% of its original activity (Figure 47).

[0291] Size exclusion chromatograph (SEC) was also used to assess the stability of various furin formulations. For SEC methods, the following equipment and materials were used:

- Agilent HPLC 1100 Series equipped with a temperature controlled autosampler and a Photo-Diode Array detector
- Autosampler 100 µL polypropylene vials
- Size Exclusion Chromatography column from TOSOH Bioscience, TSKgel
- G3000SWxl, 7.8 mm ID x 30 cm, 5 µm

In addition, following conditions were used for the SEC method:

- Mobile Phase: 50 mM MOPS, 200 mM sodium sulfate, 0.02% sodium azide, pH 7.0
- Flow Rate: 0.5 mL/min
- Run Time: 30 min
- Sample Volume: 100 µL
- Autosampler Temperature: 4°C
- Column Temperature: Ambient

[0292] Single wavelength absorption at 280 nm (Reference off) was used to create chromatographs. After manual integration, the height of the main peak at 19 min, corresponding to the rfurin content of the formulation, was used to evaluate stability. The reason for using the peak height instead of the peak area was that the chromatographic peaks were often not baseline separated, which could lead to large errors. Only one injection of each sample was conducted. Repeated analyses of the rfurin control formulation showed less than 2% variation in the peak height (data not shown).

[0293] The SEC results correlated with the furin activity assay results reported above. Analyses by SEC (Figure 2) show that the height of the rfurin monomer peak (retention time 19 min) of the control formulation decreased with the time of incubation for all temperatures. The rate of the rfurin monomer peak decrease was relatively low in the samples incubated at room temperature, as 82% of the peak height remained after seven days of incubation. However, at 37°C, the height of the rfurin monomer peak dropped to 21.6%, of the original height, after seven days of incubation. At 45°C, after two days of incubation, the main peak decreased to 14.1%. Consistent with the loss of rfurin monomer content, other chromatographic peaks began to appear over time (Figure 3), corresponding to aggregates (eluting at earlier time points) and degradation products (eluting at later time points). These additional peaks indicate both degradation and aggregation of rfurin in the control formulation. Increased degradation at 37°C compared to room temperature storage was also confirmed by Western Blotting (Figure 4). rFurin degradation may be caused by proteases that were co-purified with rfurin, or by the autocatalytic activity of rfurin itself.

[0294] In contrast, SEC analysis confirmed the increased stability of test formulation #1 (Figure 48), containing trehalose, as compared to the control formulation, which does not contain a sugar or sugar alcohol. Figure 48 shows that test formulation #1 maintained 74.8% of rfurin monomer peak height of the starting solution after incubation at 37°C for 4 days, as compared to the control formulation, which maintained only 58.5% of rfurin monomer peak height of the starting solution during the same incubation.

Example 2 – Storage stability of aqueous rfurin formulations upon freeze/thaw

[0295] The stability of the control formulation and test formulations #2-6 were tested by a freeze/thaw study. Five freeze/thaw cycles were completed and samples were analyzed by the furin activity assay and SEC. Investigating the impact of freeze/thaw is important because rfurin samples in this study and rfurin BDS are stored frozen. Freeze/thaw experiments using the control formulation (n = 4) demonstrate a minor loss of furin activity (approximately 7%) after a total of five freeze/thaw cycles. While there appears to be a downward trend, this may be due to true loss of protein or a reflection of assay variability. Regardless, this data supports the ability to freeze and thaw the rFurin, not only once, but multiple times, with little to no loss of activity. Likewise, SEC analysis of the oligomeric state of furin in the control formulation showed no loss in monomeric content over the course of the freeze/thaw experiment (Figure 6).

[0296] Since rFurin is generally stored frozen, the impact of a thawing method was evaluated. Analyses by the activity assay (Figure) demonstrate no significant difference between the two thawing methods: thawing at 4°C overnight, or at room temperature for 2 hours.

[0297] Taken together, these data suggest that rfurin in the control formulation is relatively stable for short periods at room temperature. Furthermore, loss of activity upon storage at elevated temperatures correlates to both rfurin degradation and aggregation. In addition, rfurin in the control formulation retained its activity well even after five freeze/thaw cycles.

[0298] Freeze/Thaw Study of rFurin in a highly stabilized Formulation. The freeze/thaw study was carried out using the same set of samples as the previous Freeze/thaw study; the stability of rfurin in test formulations #2 (0 ppm polysorbate 80), #3 (10 ppm polysorbate 80), #4 (25 ppm polysorbate 80), #5 (50 ppm polysorbate 80), and #6 (100 ppm polysorbate 80) was evaluated. Furin in the control formulation served as a control. Consistent with the prior analysis of the control formulation, analysis of furin activity (Figure 43) demonstrated no significant loss of activity after five freeze/thaw cycles in any of the tested formulations. Analyses of the rfurin monomer content by SEC (Figures 44 and 45) demonstrated only a small trend of sample deterioration after freeze/thaw. Even after five freeze/thaw cycles, all samples retained more than 95% of their original activity.

Example 3 – Storage stability of aqueous rfurin formulations upon mechanical stress

[0299] Without being limited by theory, one potential mechanism of the agitation effect on rfurin samples is that it induces denaturation of rfurin, exposing hydrophobic surfaces. The hydrophobic surfaces are attracted to other hydrophobic surfaces, such as other denatured rFurin proteins which induces aggregation, or causing adsorption to hydrophobic surfaces on sample tubes and materials.

[0300] The agitation study was not designed to mimic the true process of rfurin use, but to overstress the sample. To be considered stabilized, a formulation of rfurin performs at least as well as the control formulation, and a highly stabilized formulation performs better than the control formulation.

[0301] The agitation study was carried out by shaking a rfurin sample in a bottle containing Teflon balls. Samples were taken after 2 and 17 hours of agitation and analyzed by furin activity assay and SEC. As shown in the results for both the furin activity assay and SEC analysis (Figures 7 and 8, respectively), rfurin in the control formulation is fairly resistant to agitation for a limited period of time. After two hours of vigorous agitation, such as might occur during a diafiltration step, more than 85% of rfurin was still active in the control formulation. However, after 17 hours of agitation, as might occur during shipping of a sample, less than 10% of the rfurin content remained active.

[0302] The effect was then tested on furin test formulations #2 to 6, which were created by spiking nine parts of a rFurin sample with one part of 500 mM HEPES, 400 mM acetic acid, 1 mM CaCl2, pH 6 plus 10% w/w trehalose plus varied amounts of polysorbate 80.

[0303] This agitation study was carried out by shaking the test rfurin formulations and control formulation containing bottles with Teflon balls for three hours. Test formulations containing the following levels of polysorbate 80 were evaluated: none, 10 ppm, 25 ppm, 50 ppm, or 100 ppm. As shown in Figure 31, polysorbate 80 in the test formulations provided significant protection to rfurin during agitation. After three hours of agitation, the activity of rFurin in the samples containing polysorbate 80 ranged from 31,499 ± 1,218 U/mL to 36,787 ± 847 U/mL, while the sample in the formulations without polysorbate 80 had 17,835 ± 1,706 U/mL of Furin

activity. The sample in the control formulation (10 mM sodium acetate, 230 mM sodium chloride, 1 mM calcium chloride, pH 6.0) had an activity of 24,368 ± 1,135 U/mL.

[0304] Analyses by SEC confirmed the beneficial effect of polysorbate 80 in this study (Figure 32). After three hours of agitation, the peak heights of rfurin in the samples containing polysorbate 80 ranged from 37.5 mAU to 35.9 mAU, while the height of the rFurin peak in the formulation without polysorbate 80 was 22.1 mAU. The height of the rFurin peak in the control formulation was 29.9 mAU. The effect of polysorbate 80 is also shown in Figures 33 and 34. The small trend suggests that the addition of 10 ppm and 25 ppm polysorbate 80, while still beneficial, is not as effective as use of 50 ppm or 100 ppm polysorbate 80. The SEC profile for the agitated sample in the control formulation (Figure 35) does not show any additional peaks compared to the non-agitated sample. This would suggest that surface adsorption was the main reason for the activity loss. However, the UV absorption spectra (Figure 36), show that the agitated sample has a slanted and elevated profile, which is a sign of light scattering and obscuration caused by the presence of aggregates. Light obscuration is generally caused by vary large aggregates that are more opaque than smaller molecules, which cause an elevation of the UV spectra. This phenomenon cannot be distinguished from absorption by a spectrophotometer because its detector measures the amount of light that passes through a sample. Since less light gets to the detector, it is reported as absorption; hence the absorption profile is elevated.

[0305] Light can also be scattered by aggregates, which would also decrease the amount of light getting into a detector. The shorter the wave length, the more light is scattered (the amount of scattered light is inversely proportional to the fourth power on the wavelength). This means that the shorter the wavelength the less light gets to a detector; hence the absorption profile is slanted. It is likely that the aggregates were present in this sample, but the SEC analysis was unable to detect them. These kinds of problems with SEC analyses are not uncommon as protein aggregates are often too large to pass through the column, or are absorbed by the column matrix. The UV absorption spectrum of the rfurin sample in the formulation without polysorbate 80 (Figure 37) shows a similar elevated profile. Again, no aggregates were detected in the SEC analysis of this sample (Figure 38). The samples formulated with polysorbate 80 show less aggregation than those without polysorbate 80 when analyzed by the UV absorption spectra (Figures 39 to 42). Although a UV spectrum cannot quantify the amount of aggregates, again, a

small trend can be observed hinting that the samples with polysorbate 80 at 50 ppm and 100 ppm were better in protecting rFurin from aggregation than 10 ppm or 25 ppm. The data suggest that polysorbate 80 included in the formulation at a level of 75 ppm would be effective, as this concentration is in the middle of a wide plateau (50-10 ppm) and would represent a robust condition.

[0306] The UV spectrophotometry analysis was conducted using the following equipment and materials:

- Agilent 8453 Spectrophotometer
- Quartz cuvette 1 cm light pathway

[0307] The spectrophotometry analysis was conducted by first placing 0.5 mL of an appropriate formulation in a cuvette and measured as a blank. Then, 0.5 mL of a rfurin sample was placed in a cuvette, and the scan was taken from 240 nm to 400 nm.

Example 4 – Impact of pH, sucrose and polysorbate 80 on rFurin stability

[0308] rFurin samples were spiked with various buffers in order to adjust the pH to 5.0, 5.5, 6.0, 7.0 and 8.0. In addition, sucrose and/or polysorbate 80 were added to the samples at pH 6.0, 7.0 and 8.0. The samples were incubated at 37°C and tested by the furin activity assay and SEC.

[0309] Both the furin activity assay (Figure 11) and SEC (Figure 12) showed that at 37°C the rfurin was more stable at pH 6.0 than at pH 5.0 or 5.5. The samples at pH 6.0, in both the control formulation (Figure 13) and in MES (Figure 14), were more stable than those formulated in pH 7.0 or 8.0 (Figures 15 and 16) when analyzed by SEC. The addition of sucrose to the samples in pH 6.0 and 7.0 had a beneficial effect on rfurin stability. The SEC analyses (Figure 17) showed that after four days of incubation at 37°C, the peak heights of the samples containing sucrose were on average at 75% of T = 0, as compared to 52% without the sucrose. Analyses by the furin activity assay confirmed the results of the SEC experiments (Figures 18 and 19). The addition of sucrose improved rfurin stability in both the control formulation and in MES pH 6.0 (Figures 18 and 19), with similar stability seen using either buffer (Figure 20). The effects of polysorbate 80 on rfurin stability in a sucrose-containing formulation at 37°C were minimal, if any, as shown in Figures 17, 18, and 19.

[0310] These data suggest that at 37°C rfurin is most stable in the pH 6.0 formulations compared to pH 5.0, 5.5, 7.0 and 8.0. The data further show that sucrose had a beneficial effect on rfurin stability at 37°C. In addition, no significant difference was seen in rfurin stability between the control buffer (acetate) or MES at pH 6.0 in the presence of 10% sucrose. Finally, there was no significant effect of polysorbate 80 on rfurin stability in a sucrose formulation at 37°C.

Example 5 – Comparison of furin formulation stability in sucrose and mannitol

[0311] As seen in Example 4, the addition of sucrose slowed down rfurin degradation and/or activity loss at 37°C. While sucrose is not used in downstream applications such as the rVWF process, other sugars and/or sugar alcohols are, such as mannitol. The addition of mannitol to the rfurin formulation, rather than sucrose, would therefore not introduce a new raw material to the vWF process. This study was conducted to determine whether the addition of mannitol would have a beneficial effect on rfurin stability. The test formulation also possessed an improved buffering capacity by addition of HEPES and acetic acid to final concentrations of 50 mM each at pH 6.0. A stabilized formulation was created by spiking a rfurin sample with 10% of 500 mM HEPES, 400 mM acetic acid, 1 mM $CaCl_2$, pH 6, and then, adding either sucrose, mannitol, and/or polysorbate 80. Analyses by both the furin activity assay (Figure 21) and SEC (Figure 22) showed that after four days of incubation at 37°C, mannitol and sucrose had similar stabilizing effects on rfurin formulations. Again, the effect of polysorbate 80 on these formulations was not significant. Although the activity data (Figure 21) show that the sample containing mannitol and polysorbate 80 after 4 days of incubation at 37°C was better than other samples, not only does this sample not follow the overall pattern, but also the SEC analyses (Figure) did not confirm it. It is likely that this result was an outlier.

Example 6 – Comparison of Furin formulation stability in sucrose and trehalose

[0312] Various publications have shown that mannitol accelerates the denaturation of proteins during freezing, which raised some concerns about its inclusion in the rfurin formulation buffer. No such problems have been reported with trehalose, another sugar already part of the rVWF production process. This study was conducted to determine whether addition of trehalose would have a beneficial effect on rfurin stability. In addition, various concentrations of polysorbate 80

were evaluated. Analyses using the furin activity assay (Figures 23 and 24) showed that after 5 days of incubation at 37°C, the sample containing 10% sucrose retained 66.2% ±2.9% of its original activity while the sample containing 10% trehalose retained 60.1% ±4%. The difference between these samples is not significant. Both samples were significantly better in preserving rfurin activity than the control formulation, which retained only 37.5% ±4.2% of its original activity.

[0313] Analyses by SEC (Figure 25) confirmed the activity analyses. The rfurin peak for the sample in 10% sucrose retained 78.3% of its height compared to 75.1% for the sample in 10% trehalose and 44.2% for the control formulation. Also, analyses by western blotting (Figure 26) showed the least degradation in the samples containing 10% sucrose or 10% trehalose. Note that the samples are presented as pairs, with day 0 followed by day 5 for each of the formulations.

[0314] Both the furin activity assay (Figure 27) and SEC (Figure 28) analyses show that 10% trehalose was better than 5% or 2% in preserving rfurin activity at 37°C. These findings were also confirmed by western blotting (Figure 26). The impact of polysorbate 80 on rfurin stability at 37°C was minimal according to the analyses by the furin activity assay and SEC (Figures 29 and 30, respectively).

[0315] SEC and furin activity assays were conducted as described above. Western blotting was performed using the following equipment and materials:

- Goat anti-Furin (peptide) primary antibody (Cat# SC-12484) from Santa Cruz Biotechnology, Inc.
- Rabbit anti-goat IgG-HRP conjugate secondary antibody (Cat# A5420) from Sigma
- Pierce Metal Enhanced Substrate Kit containing DAB/Metal Concentrate 10X,
- Pierce (Cat# 1856090) and Stable Peroxidase Buffer, Pierce (Cat# 185591)
- 4-20% Tris-Glycine gel (Cat# EC6025BOX) from Invitrogen
- NuPAGE® Sample Reducing Agent (0.5M DTT, 10x, Cat# NP0004) from Invitrogen
- Non-Reducing Sample Buffer (4X, Cat# 84788) from Thermo
- PBS (Cat# P4417) from Sigma
- Tween 20 (Cat# 9480) from EMD Chemicals
- BSA (Cat# A7906) from Sigma
- Gel transfer device (iBLOT Cat# IB401001) from Invitrogen
- PVDF (Immobilon-P, Cat# IPVH07850) transfer membrane from Millipore

[0316] A polyclonal antibody was used in this study instead of a monoclonal to increase detection of rFurin degradation products. 5 µl of a sample was combined with 1 µl of 10x DTT, and 4 µl of 4x non-reducing dye. The sample was heated at 70°C to 75°C for 10 minutes. 10 µl of the sample was loaded to 4-20% SDS-PAGE gel, and run at 150 V for 60 to 70 minutes. The protein gel was transferred to PVDF membrane using the iBLOT at 20 V for 6 minutes. The PVDF membrane was then blocked with PBS buffer containing 0.1% TWEEN 20 and 3% BSA for 1 hour. The membrane was incubated for one hour in the primary antibody diluted 125 fold with the same buffer. The membrane was washed with PBST buffer for five minutes, three times each. The membrane was incubated for one hour in the secondary antibody diluted 10,000 fold with the same buffer as the primary antibody. The incubation time was 1 hour. The blot was washed using PBST buffer for five minutes, three times each. The blot was developed in 10 mL of premixed chromagenic substrate (1 ml concentrate plus 9 ml of Stable Peroxidase Buffer) followed by the wash with water for 10 minutes.

Example 7 – Effects of stabilizing agents upon dilution of furin compositions

[0317] The rFurin dilution study was carried out to compare a starting formulation and its diluent to a stabilized formulation and a stabilized diluent. The study mimicked the dilution method that used in the rVWF maturation process. Briefly, rfurin BDS was passed through a filter followed by the addition of a 200-fold volume of the diluent. The main difference between the test dilution method and the starting dilution method is that in the test (highly stabilized) method, 75 ppm polysorbate 80 is present in both the rfurin BDS and the diluent, while in the starting method, there is no polysorbate 80 in either the rfurin BDS or the diluent.

[0318] Two dilution experiments were carried out, and both have shown that the combination of the stabilized formulation with its stabilized diluent was superior to the starting furin and diluent formulations. In the first experiment, the test method using the stabilized formulations recovered 83% to 87% of the expected rfurin activity, while the control methods recovered only 21% to 22% (Table 18). In this experiment, the rfurin sample was passed through a filter and followed by a 200-fold volume of a diluent. The filtrate was collected to a bag and then transferred to a graduated cylinder.

Table 18. Experimental results of rfurin dilution experiments performed with and without non-ionic surfactant.

Sample		Activity (IU)	St. Dev.	Dilution Factor	Expected Activity (IU)	Recovery (% Activity)
Starting Material		25,953	1,118	1	N/A	N/A
Control Formulation After Filtration	From a Bag	27.264	2.815	200	129.8	21.0
	From a Cylinder	28.3	1.56	200	129.8	21.8
New Formulation After Filtration	From a Bag	108.137	6.611	200	129.8	83.3
	From a Cylinder	113.4	5.21	200	129.8	87.4

[0319] In the second experiment, the test method recovered 80% of the expected rfurin activity, while the control method recovered only 27% (Table 19). In this experiment, the rfurin sample was passed through a filter and followed by a 200-fold volume of a diluent. The filtrate was collected to a cylinder. The combination of the stabilized rfurin formulation and the stabilized diluent increased rfurin recovery three to four times compared to the control method. The improved recovery is, without being limited by theory, linked to the presence of polysorbate 80.

Table 19. Experimental results of rfurin dilution experiments performed with and without non-ionic surfactant.

Sample	Activity (IU)	St. Dev.	Dilution Factor	Expected Activity (IU)	Recovery (% Activity)
Starting Material	32,379	1,654	N/A	N/A	N/A
Control Formulation After Filtration	44.267	1.607	200	161.9	27.3
New Formulation After Filtration	129.646	11.514	200	161.9	80.1

Example 8 – Characteristics of stabilized formulation stock buffer

[0320] The stock buffer for the stabilized rfurin formulation (500 mM HEPES, 400 mM acetic acid, 1 mM $CaCl_2$, pH 6.0) can be made consistently (Table 20). The RSD's for pH and conductivity were < 0.3%. The pH was slightly and indirectly correlated with temperature, dropping 0.014 units per degree Celsius, while conductivity was directly correlated with temperature, raising 0.40 mS/cm per degree C (Figure 49). The average temperature of the samples when the pH and conductivity were measured was 27.6 °C. In manufacturing, the samples are read at 25±0.5°C. Based on the linear regressions in Figure 48, the expected pH and conductivity at 25°C were calculated. The relative standard deviation from Table 20 was applied

to this value to determine the expected range (±3 sd). pH at 25°C is expected to be 6.04 (±0.01). Conductivity at 25°C is expected to be 19.9±0.2 mS/cm. These expected ranges are based on three lots made under limited circumstances. The specification ranges for the buffer need not be set this strictly. The pH specification will be the same as the final BDS pH specification, 5.90-6.10. The conductivity range will be similar to that used for the previous BDS buffer, *e.g.*, with a range of ±20%, for a specification of 15.9-23.9 mS/cm. The requirements of the rVWF process are generally not of concern in setting the buffer specifications because the rfurin will be diluted 200-fold in the rVWF process. Experimental data in Table 21 and Table 22 correspond to the graphs presented in Figure 49.

Table 20. Characteristics of stabilized formulation stock buffer.

Reagent	Buffer 1	Buffer 2	Buffer 3					
Water, L	0.85	0.85	0.85					
HEPES, g	119.15	119.15	119.15					
CaCl2, g	0.111	0.111	0.111					
Acetic acid, mL	23	23	23					
10M NaOH, mL	39.4	39.4	39.4	mean	sd	rsd, %	mean + 3 sd	mean - 3 sd
pH	6.011	6.003	6.005	6.006	0.004	0.07	6.019	5.994
Cond., mS/cm	21.23	21.15	21.11	21.16	0.06	0.29	21.35	20.98
Temp., C	27.5	27.6	27.6	27.6	0.06	0.21	27.7	27.4

Table 21. Dependence of stock buffer conductivity on temperature.

Temp, C	Cond, mS/cm
18	17.23
18.4	17.42
18.7	17.53
19	17.63
19.3	17.75
19.6	17.86
19.7	17.91
20	18.03
20.2	17.72
20.5	17.83
21.6	17.86
24.4	19.81
27.6	21.1

Table 22. Dependence of stock buffer pH on temperature.

Temp, C	pH
18	6.135
19.3	6.103
21.6	6.088
27.6	6.005

REFERENCES

[0321] All references cited herein are hereby incorporated by reference herein in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[0322] Many modifications and variations of this application can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the application is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which the claims are entitled.

WHAT IS CLAIMED:

1. A stabilized aqueous composition of recombinant furin (rfurin), the composition comprising:

(a) from 8,000 U/mL to 500,000 U/mL rfurin;

(b) from 100 mM to 300 mM of a pharmaceutically acceptable salt;

(c) from 0.5 mM to 2 mM calcium;

(d) from 2% to 20% sugar or sugar alcohol;

(e) from 10 to 200 ppm non-ionic surfactant;

(f) from 10 to 200 mM buffering agent; and

(g) a pH from 5.5 to 7.5.

2. The composition of claim 1, comprising from 150 mM to 250 mM of a pharmaceutically acceptable salt.

3. The composition of claim 2, comprising 190±10 mM of a pharmaceutically acceptable salt.

4. The composition of claim 3, comprising 190 mM of a pharmaceutically acceptable salt.

5. The composition according to any one of claims 1 to 4, wherein the pharmaceutically acceptable salt is sodium chloride.

6. The composition according to any one of claims 1 to 4, wherein the pharmaceutically acceptable salt is potassium chloride.

7. The composition according to any one of claims 1 to 6, comprising 0.9±0.2 mM calcium.

8. The composition of claim 7, comprising 0.92 mM calcium.

9. The composition according to any one of claims 1 to 8, comprising from 5% to 15% sugar or sugar alcohol.

10. The composition of claim 9, comprising 10±2% sugar or sugar alcohol.

11. The composition of claim 10, comprising 10% sugar or sugar alcohol.

12. The composition according to any one of claims 1 to 11, wherein the sugar or sugar alcohol is selected from the group consisting of sucrose, trehalose, mannitol, and a combination thereof.

13. The composition according to any one of claims 1 to 11, wherein the sugar or sugar alcohol is trehalose.

14. The composition according to any one of claims 1 to 11, wherein the sugar or sugar alcohol is sucrose.

15. The composition according to any one of claims 1 to 14, comprising from 10 ppm to 100 ppm non-ionic surfactant.

16. The composition of claim 15, comprising from 50 ppm to 100 ppm non-ionic surfactant.

17. The composition of claim 16, comprising 75 ppm non-ionic surfactant.

18. The composition according to any one of claims 1 to 17, wherein the non-ionic surfactant is polysorbate-80.

19. The composition according to any one of claims 1 to 18, comprising from 50 mM to 150 mM buffering agent.

20. The composition of claim 19, comprising 90±10 mM buffering agent.

21. The composition of claim 20, comprising 91 mM buffering agent.

22. The composition according to any one of claims 1 to 21, wherein the buffering agent comprises acetate.

23. The composition according to any one of claims 1 to 21, wherein the buffering agent comprises HEPES.

24. The composition according to any one of claims 1 to 21, wherein the buffering agent comprises MES.

25. The composition according to any one of claims 1 to 21, wherein the buffering agent comprises acetate and HEPES.

26. The composition of claim 25, comprising from 25 mM to 75 mM acetate and from 25 to 75 mM HEPES.

27. The composition of claim 26, comprising 45±5 mM acetate and 45±5 mM HEPES.

28. The composition of claim 27, comprising 45 mM acetate and 46 mM HEPES.

29. The composition according to any one of claims 1 to 28, having a pH from 5.5 to 7.0.

30. The composition of claim 29, having a pH from 5.5 to 6.5.

31. The composition of claim 30, having a pH of 6.0±0.2.

32. The composition of claim 31, having a pH of 6.0.

33. The composition according to any one of claims 1 to 32, wherein the composition has increased stability when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

34. The composition of claim 33, wherein the composition maintains a higher percentage of rfurin activity when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

35. The composition of claim 33 or 34, wherein the composition maintains a higher percentage of rfurin monomer content when stored at 37°C as compared to a rfurin composition that does not contain a sugar or sugar alcohol.

36. The composition according to any one of claims 1 to 35, wherein the composition has increased stability when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

37. The composition of claim 36, wherein the composition maintains a higher percentage of rfurin activity when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

38. The composition of claim 36 or 37, wherein the composition maintains a higher percentage of rfurin monomer content when agitated as compared to a rfurin composition that does not contain a non-ionic surfactant.

39. The composition according to any one of claims 1 to 38, wherein the composition has increased stability when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

40. The composition of claim 39, wherein the composition maintains a higher percentage of rfurin activity when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

41. The composition of claim 39 or 40, wherein the composition maintains a higher percentage of rfurin monomer content when diluted as compared to a rfurin composition that does not contain a non-ionic surfactant.

42. A stabilized aqueous composition of recombinant furin (rfurin), the composition comprising:

(a) from 8,000 U/mL to 500,000 U/mL rfurin;

(b) 190 mM sodium chloride;

(c) 0.92 mM calcium;

(d) 10% trehalose;

(e) 75 ppm polysorbate 80;

(f) 45 mM acetic acid;

(g) 46 mM HEPES; and

(g) a pH from 5.5 to 7.5.

43. The composition of claim 42, having a pH from 5.5 to 7.0.

44. The composition of claim 42, having a pH from 5.5 to 6.5.

45. The composition of claim 42, having a pH of 6.0±0.2.

46. The composition of claim 42, having a pH of 6.0.

47. A method for diluting an aqueous rfurin composition, the method comprising adding a dilution buffer comprising from 10 ppm to 200 ppm of a non-ionic surfactant to the aqueous rfurin composition, thereby forming a diluted rfurin composition.

48. The method of claim 43, wherein the dilution buffer comprises from 10 ppm to 100 ppm of a non-ionic surfactant.

49. The method of claim 48, wherein the dilution buffer comprises from 50 ppm to 100 ppm of a non-ionic surfactant.

50. The method of claim 49, wherein the dilution buffer comprises 75 ppm of a non-ionic surfactant.

51. The method according to any one of claims 43 to 50, wherein the dilution buffer has a pH of from 5.5 to 7.5.

52. The method of claim 51, wherein the dilution buffer has a pH of from 5.5 to 6.5.

53. The method of claim 52, wherein the dilution buffer has a pH of 6.0±0.2.

54. The method of claim 53, wherein the dilution buffer has a pH of 6.0.

55. The method according to any one of claims 43 to 51, wherein the diluted rfurin composition comprises at least 50% of rfurin activity present in the aqueous rfurin composition prior to dilution.

56. The method of claim 55, wherein the diluted rfurin composition comprises at least 75% of rfurin activity present in the aqueous rfurin composition prior to dilution.