

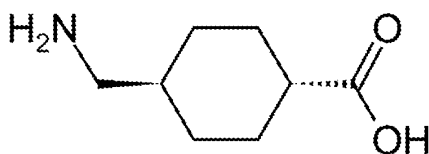
PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

Pharmaceutical compositions comprising tranexamic acid are provided. The compositions
5 are suitable for the treatment of haemorrhage and may be administered intramuscularly.

BACKGROUND OF THE INVENTION

Tranexamic acid (TXA) is an antifibrinolytic agent that inhibits the breakdown of fibrin clots
by blocking the binding of plasminogen and plasmin to fibrin. TXA is a synthetic lysine amino
10 acid derivative which acts to prevent haemorrhage and reduce bleeding. TXA is commercially
available in a tablet form (Cyklokapron 500 mg) and in an injectable intravenous form
(Cyklokapron 100 mg/mL). TXA is used to treat and prevent bleeding and is most effective
when given soon after injury. Delaying treatment with TXA reduces its lifesaving potential.



Structure of TXA

In response to trauma, TXA is usually administered by intravenous injection; however,
securing an intravenous line can take time and the drug must be injected slowly. Thus, there
20 is a desire for improved ways of administering TXA.

In a pharmacokinetic study, trauma patients who had received a 1 g dose of TXA
intravenously received a further 1 g dose intramuscularly at least 90 minutes after the
intravenous dose. The intramuscular dose was given as two 5 mL injections (0.5 g of TXA in
25 each injection) into the thigh, gluteal, or deltoid muscles. This study found that in bleeding
trauma patients, intramuscular TXA is well tolerated and rapidly absorbed (Grassin-Delyle *et al.*
Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical
trial. Br J Anaesth. 2021 Jan;126(1):201-209. doi: 10.1016/j.bja.2020.07.058).

US 2023/0248643A1 refers to concentrated injectable tranexamic acid compositions and methods of use thereof. WO 2024/023813A1 refers to a method for enhancing solubility of tranexamic acid that involves initially dissolving tranexamic acid in water.

5 SUMMARY OF THE INVENTION

The present invention aims to improve upon the prior art by providing stable pharmaceutical compositions comprising TXA that can be administered in a single lower volume intramuscular injection thereby improving administration of a therapeutically effective dose of TXA for the treatment or prevention of haemorrhage.

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The invention provides an aqueous pharmaceutical composition comprising tranexamic acid (TXA) or a pharmaceutically acceptable salt thereof, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is greater than about 0.637 M, wherein the pH of the composition is about 3 to about 5.

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The concentration of TXA or pharmaceutically acceptable salt thereof in the composition may be greater than 1.06 M, at least about 1.27 M, at least about 1.59 M, at least about 1.91 M, at least about 2.23 M, at least about 2.54 M or at least about 2.86 M. The concentration of TXA or pharmaceutically acceptable salt thereof in the composition may be no more than about 3.18 M, no more than about 3.50 M, no more than about 3.68 M or no more than about 3.82 M. The concentration of TXA or pharmaceutically acceptable salt thereof in the composition may be within about a 25% range around 2.9 M or about 2.54 M to about 3.18 M. The composition may comprise TXA at a concentration within about a 25% range around 455 mg/mL.

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The pH of the composition may be about 3.5 to about 4.5 or about 3.75 to about 4.25, preferably about 4. The composition may comprise a pH modifying agent, optionally wherein the pH modifying agent is an acid. The composition may be substantially free from a pharmaceutical excipient, optionally wherein the pharmaceutical excipient is a solubilizing agent.

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The composition may be for parenteral administration, preferably for intramuscular administration. The composition may be for use in the treatment or prevention of a disease or disorder in a subject. The composition may be for use in treating or preventing

haemorrhage in a subject. The composition may be administered parenterally to the subject, optionally intramuscularly to the subject. The amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject may be within about a 10% range around 6.36 mmol. The composition may comprise TXA and the amount of TXA administered to the subject may be within about a 10% range around 1g. The composition may be administered to the subject in a single dose. The volume of the composition administered to the subject may be no more than about 5 mL in total, no more than about 4 mL in total, no more than about 3 mL in total, about 1.5 mL to about 2.5 mL in total, about 2 mL to about 2.5 mL in total, preferably about 2.2 mL in total. The subject may not have been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24 hours, 12 hours, 6 hours, 3 hours, 1.5 hours, 1 hour or 0.5 hours. Preferably, the subject has not been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24 hours.

The invention provides a container containing one dose or a plurality of doses of the composition according to the invention. The amount of TXA or a pharmaceutically acceptable salt thereof in a dose may be within about a 10% range around 6.36 mmol. The composition may comprise TXA and the amount of TXA in a dose may be within about a 10% range around 1g.

The invention provides an injection device for single or multiple use, wherein the injection device comprises an injection needle and a container according to the invention. The injection device may be for parenteral administration of the pharmaceutical composition, preferably for intramuscular administration. Preferably, the injection device is for single use.

The invention provides a method of preparing a composition according to the invention, wherein the method comprises:

(a) providing an aqueous acid solution; and

(b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid solution,

optionally wherein the method further comprises adding concentrated acid, further aqueous acid solution, base and/or water until the pH of the solution reaches about 3 to about 5, preferably about 4.

The acid may be an inorganic acid or organic acid, preferably an inorganic acid such as hydrochloric acid.

5 The invention provides a method of preparing a container according to the invention, wherein the method comprises:

- A) (a) sterilising an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof; and
(b) adding the sterilised solution comprising TXA or a pharmaceutically acceptable salt thereof to a (sterilised) container; or
- 10 B) (a) adding an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof to a container; and
(b) sterilising the container with the aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof comprised therein.

15 DETAILED DESCRIPTION OF THE INVENTION

It should be appreciated that options described in relation to one area of improvement will apply *mutatis mutandis* to other areas.

Pharmaceutical compositions

20 The invention provides a composition, in particular a pharmaceutical composition, comprising tranexamic acid (TXA) or a pharmaceutically acceptable salt thereof. The pharmaceutical composition may be aqueous, preferably an aqueous solution in which the TXA or pharmaceutically acceptable salt thereof is entirely dissolved. For administration to a subject the pharmaceutical composition will necessarily be liquid; however, the pharmaceutical
25 composition may be stored frozen and thawed prior to administration.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be greater than about 0.637 M, greater than about 1.06 M, at least about 1.27 M, at least about 1.59 M, at least about 1.91 M, at least about 2.23 M, at least about
30 2.54 M or at least about 2.86 M, preferably at least about 2.86 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be no more than about 3.18 M, no more than about 3.50 M, no more than about 3.68 M or no more than about 3.82 M, preferably no more than about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 1.27 M to about 3.18 M, about 1.27 M to about 3.50 M, about 1.27 M to about 3.68 M or about 1.27 M to about 3.82 M, preferably about 1.27 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 1.59 M to about 3.18 M, about 1.59 M to about 3.50 M, about 1.59 M to about 3.68 M or about 1.59 M to about 3.82 M, preferably about 1.59 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 1.91 M to about 3.18 M, about 1.91 M to about 3.50 M, about 1.91 M to about 3.68 M or about 1.91 M to about 3.82 M, preferably about 1.91 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 2.23 M to about 3.18 M, about 2.23 M to about 3.50 M, about 2.23 M to about 3.68 M or about 2.23 M to about 3.82 M, preferably about 2.23 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 2.54 M to about 3.18 M, about 2.54 M to about 3.50 M, about 2.54 M to about 3.68 M or about 2.54 M to about 3.82 M, preferably about 2.54 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be about 2.86 M to about 3.18 M, about 2.86 M to about 3.50 M, about 2.86 M to about 3.68 M or about 2.86 M to about 3.82 M, preferably about 2.86 M to about 3.18 M.

The concentration of TXA or pharmaceutically acceptable salt thereof in the pharmaceutical composition may be within about a 25%, 20%, 15%, 10% or 5% range around 2.9 M, preferably within about a 10% range around 2.9 M, more preferably within about a 5% range

around 2.9 M. Thus, the concentration of TXA or pharmaceutically acceptable salt thereof may be about 2.18 M to about 3.63 M, about 2.32 M to about 3.48 M, about 2.47 M to about 3.34 M, about 2.61 M to about 3.19 M or about 2.76 M to about 3.05 M, preferably about 2.61 to about 3.19 M, more preferably about 2.76 M to about 3.05 M.

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The concentration of TXA in the pharmaceutical composition may be greater than 100 mg/mL, greater than 167 mg/mL, at least about 200 mg/mL, at least about 250 mg/mL, at least about 300 mg/mL, at least about 350 mg/mL, at least about 400 mg/mL or at least about 450 mg/mL, preferably at least about 450 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be no more than about 500 mg/mL, no more than about 550 mg/mL, no more than about 578 mg/mL or no more than about 600 mg/mL, preferably no more than about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be about 200 mg/mL to about 500 mg/mL, about 200 mg/mL to about 550 mg/mL, about 200 mg/mL to about 578 mg/mL or about 200 mg/mL to about 600 mg/mL, preferably about 200 mg/mL to about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be about 250 mg/mL to about 500 mg/mL, about 250 mg/mL to about 550 mg/mL, about 250 mg/mL to about 578 mg/mL or about 250 mg/mL to about 600 mg/mL, preferably about 250 mg/mL to about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be about 300 mg/mL to about 500 mg/mL, about 300 mg/mL to about 550 mg/mL, about 300 mg/mL to about 578 mg/mL or about 300 mg/mL to about 600 mg/mL, preferably about 300 mg/mL to about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be about 350 mg/mL to about 500 mg/mL, about 350 mg/mL to about 550 mg/mL, about 350 mg/mL to about 578 mg/mL or about 350 mg/mL to about 600 mg/mL, preferably about 350 mg/mL to about 500 mg/mL.

The concentration of TXA in the pharmaceutical composition may be about 400 mg/mL to about 500 mg/mL, about 400 mg/mL to about 550 mg/mL, about 400 mg/mL to about 578 mg/mL or about 400 mg/mL to about 600 mg/mL, preferably about 400 mg/mL to about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be about 450 mg/mL to about 500 mg/mL, about 450 mg/mL to about 550 mg/mL, about 450 mg/mL to about 578 mg/mL or about 450 mg/mL to about 600 mg/mL, preferably about 450 mg/mL to about 500 mg/mL.

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The concentration of TXA in the pharmaceutical composition may be within about a 25%, 20%, 15%, 10% or 5% range around 455 mg/mL, preferably within about a 10% range around 455 mg/mL, more preferably within about a 5% range around 455 mg/mL. Thus, the concentration of TXA may be about 341 mg/mL to about 569 mg/mL, about 364 mg/mL to about 546 mg/mL, about 387 mg/mL to about 523 mg/mL, about 410 mg/mL to about 501 mg/mL or about 432 mg/mL to about 478 mg/mL, preferably about 410 mg/mL to about 501 mg/mL, more preferably about 432 mg/mL to about 478 mg/mL. The concentration of TXA in the pharmaceutical composition may be 455 mg/mL.

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The pH of the pharmaceutical composition may be about 3 to about 5, about 3.5 to about 4.5 about 3.75 to about 4.25, about 3.85 to about 4.15, about 3.9 to about 4.1, preferably about 3.5 to about 4.5, more preferably about 4.

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The pH of the pharmaceutical composition may be at least about 1, at least about 2, at least about 3, at least about 3.5, at least about 3.75, at least about 3.85 or at least about 3.9, preferably at least about 3.5.

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The pH of the pharmaceutical composition may be no more than about 4.1, no more than about 4.15, no more than about 4.25, no more than about 4.5, no more than about 5, no more than about 6, no more than about 7, preferably not more than about 4.5.

The pharmaceutical composition may comprise TXA or a pharmaceutically acceptable salt thereof, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the

composition is greater than about 0.637 M, wherein the pH of the composition is about 3 to about 5, preferably about 4.

5 The pharmaceutical composition may comprise TXA or a pharmaceutically acceptable salt thereof, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is within about a 25% range around 2.9 M, wherein the pH of the composition is about 3 to about 5, preferably about 4.

10 The pharmaceutical composition may comprise TXA, wherein the concentration of TXA in the composition is within about a 25% range around 455 mg/mL, wherein the pH of the composition is about 3 to about 5, preferably about 4.

15 The pharmaceutical composition may comprise a pH modifying agent. The pH modifying agent may be present in an amount such that the pH of the composition is as described herein (for example about 3 to about 5, preferably about 4). The pH modifying agent may comprise one or more acids and/or bases. The pH modifying agent may comprise one or more acids. Acids may be inorganic or organic, preferably inorganic. Acids may be monoprotic or polyprotic, preferably monoprotic.

20 Inorganic acids include, but are not limited to, boric acid, hydrochloric acid, nitric acid, metaphosphoric acid, phosphoric acid, sulfuric acid and sulfurous acid. Preferably, the inorganic acid is hydrochloric acid.

25 Organic acids include, but are not limited to, organic compounds comprising carboxylic or sulfonic acid groups such as acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, citric acid, edetic acid, formic acid, fumaric acid, gentisic acid, gluconic acid, hydroxyethylpiperazine ethane sulfonic acid, isostearic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, myristic acid, oleic acid, palmitic acid, pentetic acid, propionic acid, succinic acid and tartaric acid.

30 The concentration of acid may be about 1N to about 9N, about 2N to about 8N, about 3N to about 7N, about 4N to about 6N, about 4N to about 5N, preferably about 4N to about 6N, more preferably about 4N to about 5N.

Bases include, but are not limited to, hydroxides, oxides, phosphates, sulfates, carbonates and silicates of lithium, sodium, calcium, potassium, magnesium and aluminium. Preferably, the base comprises sodium hydroxide.

- 5 The pharmaceutical composition may comprise TXA or a pharmaceutically acceptable salt thereof and a pH modifying agent, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is greater than about 0.637 M, wherein the pH of the composition is about 3 to about 5, preferably about 4, and wherein the pH modifying agent is an inorganic acid such as hydrochloric acid.

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The pharmaceutical composition may comprise TXA or a pharmaceutically acceptable salt thereof and a pH modifying agent, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is within about a 25% range around 2.9 M, wherein the pH of the composition is about 3 to about 5, preferably about 4, and wherein the pH modifying agent is an inorganic acid such as hydrochloric acid.

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The pharmaceutical composition may comprise TXA and a pH modifying agent, wherein the concentration of TXA in the composition is within about a 25% range around 455 mg/mL, wherein the pH of the composition is about 3 to about 5, preferably about 4, and wherein the pH modifying agent is an inorganic acid such as hydrochloric acid.

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The pharmaceutical composition may be aqueous and consist of TXA or a pharmaceutically acceptable salt thereof and a pH modifying agent, preferably an inorganic acid such as hydrochloric acid. Thus, the pharmaceutical composition may be an aqueous pharmaceutical composition comprising TXA and hydrochloric acid, wherein the concentration of TXA in the composition is within about a 25% range around 455 mg/mL, wherein the pH of the composition is about 3 to about 5, preferably about 4.

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The pharmaceutical composition may or may not include a pharmaceutical excipient. The pharmaceutical composition may be substantially free from a pharmaceutical excipient. The pharmaceutical composition may be substantially free from a pharmaceutical excipient excepting any specifically required by the claims. The pharmaceutical composition may comprise a pH modifying agent but be substantially free from any other pharmaceutical excipient. The pharmaceutical composition may comprise a buffering agent but be

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substantially free from any other pharmaceutical excipient. The pharmaceutical composition may comprise a pH modifying agent and buffering agent but be substantially free from any other pharmaceutical excipient. The pharmaceutical composition may comprise a buffering agent but be substantially free from any other pharmaceutical excipient in particular a
5 solubilizing agent.

A pharmaceutical excipient may be a pharmacologically suitable and therapeutically useful substance which is not an active substance. Excipients generally have no pharmacological activity, or at least no undesirable pharmacological activity.
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Pharmaceutical excipients include, but are not limited to, co-solvents, solubilizing agents, antimicrobial agents, buffering agents, antioxidants, and tonicity adjusting agents.

The pharmaceutical composition may be substantially free from any one or more of co-solvents, solubilizing agents, antimicrobial agents, buffering agents, antioxidants, and tonicity
15 adjusting agents. The pharmaceutical composition may be substantially free from solubilizing agents, antimicrobial agents, buffering agents, antioxidants, and tonicity adjusting agents. The pharmaceutical composition may be substantially free from co-solvents, antimicrobial agents, buffering agents, antioxidants, and tonicity adjusting agents.
20 The pharmaceutical composition may be substantially free from co-solvents, solubilizing agents, buffering agents, antioxidants, and tonicity adjusting agents. The pharmaceutical composition may be substantially free from co-solvents, solubilizing agents, antimicrobial agents, antioxidants, and tonicity adjusting agents. The pharmaceutical composition may be substantially free from co-solvents, solubilizing agents, antimicrobial agents, buffering
25 agents, and tonicity adjusting agents. The pharmaceutical composition may be substantially free from co-solvents, solubilizing agents, antimicrobial agents, buffering agents and antioxidants. Preferably, the pharmaceutical composition is substantially free from a solubilizing agent.

30 Co-solvents may include solvents that are miscible in water and may include hydroxylated solvents such as alcohols (e.g. ethanol, isopropyl alcohol, glycerol, sorbitol), glycols (e.g. polyethylene glycol, propylene glycol), dimethylsulfoxide, dimethylacetamide and/or any other co-solvents known to those of skill in the art. The pharmaceutical composition may be substantially free from co-solvents.

Solubilizing agents may include co-solvents or amphiphilic molecules that can interact with hydrophobic and hydrophilic compounds. These may include non-ionic polyoxyethylene fatty acids (e.g. polysorbates or Tweens). In particular, polysorbates 20 (polyoxyethylene sorbitan monolaurate) and 80 (polyoxyethylene sorbitan monooleate). Solubilizing agents may also include complexing agents which include cyclodextrins such as Captisol (SBE- β -CD, Sulfobutylether- β -Cyclodextrin). Solubilizing agents may include any solubilizing agent known to those of skill in the art. The pharmaceutical composition may be substantially free from solubilizing agents.

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Solubilizing agents may include propylene glycol, polyethylene glycol (such as PEG 300), glycerol, polyethoxylated castor oil (such as Kolliphor EL; CAS number 61791-12-6) and cyclodextrin (such as Captisol; Sulfobutylether- β -Cyclodextrin). Kolliphor EL is a non-ionic solubilizer and emulsifier made by reacting castor oil with ethylene oxide in a molar ratio of 1:35.

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The pharmaceutical composition may be substantially free from propylene glycol, polyethylene glycol (such as PEG 300), glycerol, polyethoxylated castor oil (such as Kolliphor EL; CAS number 61791-12-6) and cyclodextrin (such as Captisol; Sulfobutylether- β -cyclodextrin).

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Antimicrobial agents may include antibacterial and antifungal agents such as benzyl alcohol, phenoxyethanol, parabens, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol and/or any other antimicrobial agents known to those of skill in the art. The pharmaceutical composition may be substantially free from antimicrobial agents.

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Buffering agents may resist pH change upon addition of acidic or basic components. Buffering agents include, but are not limited to, citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, Mclivaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris-(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'

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bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2- hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxy- methyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-amino- ethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methyl- amino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethyl- aminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxy- propanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropane- sulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)-piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxy- methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2- hydroxyethylglycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4- butanesulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-amino- propanesulfonic acid), AMPD (2-amino-2-methyl-1,3~propanediol), and/or any other buffers known to those of skill in the art.

The buffering agent may be acetate buffer, citrate buffer and/or phosphate buffer, preferably phosphate buffer. Buffering agent concentrations may include from about 0.01 mM to about 150 mM, from about 1 mM to about 150 mM, from about 5 mM to about 150 mM, from about 10 mM to about 150 mM, from about 20 mM to about 150 mM, from about 1 mM to about 100 mM, from about 5 mM to about 100 mM, from about 10 mM to about 100 mM, from about 20 mM to about 100 mM, from about 1 mM to about 50 mM, from about 5 mM to about 50 mM, from about 10 mM to about 50 mM, from about 20 mM to about 50 mM. Preferably, buffering agent concentrations are from about 20 mM to about 50 mM.

Antioxidants may prevent drug oxidation and may include ascorbic acid, salts of sulfurous acid (e.g sodium bisulfite, sodium metabisulfite or sodium thiosulfate), thiols (e.g. thioglycerol and thioglycolic acid) and/or any other antioxidant known to those of skill in the art.

Tonicity adjusting agents may refer to substances used to render a solution isotonic, meaning similar in osmotic pressure to the osmotic pressure of biological cells. Tonicity adjusting agents may be organic or inorganic tonicity adjusting agents. Tonicity adjusting agents may include electrolytes such as sodium chloride, mono- and di- saccharides (e.g. dextrose, sucrose), glycerin and mannitol. Tonicity adjusting agents may include, but are not limited to,

ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium
5 monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium
10 cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine, zinc sulfate and/or any other tonicity adjusting agent known to those of skill in the art.

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Pharmaceutical excipients may include the substances listed in the FDA Inactive Ingredient Database (<https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>).

20 The pharmaceutical composition may be substantially free from inorganic salts. Inorganic salts include, but are not limited to, salts of lithium, sodium, potassium, magnesium, calcium and aluminium for example fluoride, chloride, bromide, iodide, hydroxide, nitrate, sulfate, carbonate, bicarbonate and phosphate. Preferably, the pharmaceutical composition is substantially free from NaCl.

25 The pharmaceutical composition may be substantially free from electrolyte solution (such as 0.9% NaCl or Ringer's solution), carbohydrate solution (such as 5% glucose solution), amino acid solution or dextran solution (such as dextran 40 and dextran 70). Preferably, the pharmaceutical composition is substantially free from 0.9% NaCl solution.

30 The pharmaceutical composition may be substantially free from active pharmaceutical ingredients other than TXA. Thus, the pharmaceutical composition may be substantially free from anticoagulants (such as heparin) or clotting factors.

The pharmaceutical composition may be substantially free from cellulose microcrystalline, colloidal silica anhydrous, hydroxypropylcellulose, magnesium stearate, povidone and/or talcum. The pharmaceutical composition may be substantially free from micelle forming vehicles such as liposomes.

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The pharmaceutical compositions are preferably aqueous and thus comprise water. The water may meet the standards of purity for Water For Injection (WFI) and/or Sterile Water For Injection (SWFI). Water and all other components in the pharmaceutical composition may meet the requirements of the relevant United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur), British Pharmacopoeia (BP), and/or Japanese Pharmacopoeia (JP) monographs.

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The pharmaceutical composition may be clear and/or colourless.

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The pharmaceutical composition may be stable at 25 °C or 40 °C for at least 1 month, at least 2 months, at least 3 months or at least 12 months, preferably at least 3 months. By stable, it is meant that 100% or at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of the initial amount of active pharmaceutical ingredient (i.e. TXA or a pharmaceutically acceptable salt thereof) is present in the pharmaceutical composition. Preferably, at least 95% of the initial amount of active pharmaceutical ingredient is present.

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Medical uses

All aspects and embodiments described in relation to the other aspects of the invention (in particular the pharmaceutical compositions) apply *mutatis mutandis* to the related medical uses described below.

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The invention also relates to a pharmaceutical composition as described herein for use as a medicament. Thus, the invention provides a pharmaceutical composition described herein for use in the treatment or prevention of a disease or disorder in a subject. The invention provides a method for treating or preventing a disease or disorder in a subject, the method comprising administering to the subject a pharmaceutical composition described herein. The invention provides a use of a pharmaceutical composition described herein in the manufacture of a medicament for the treatment or prevention of disease in a subject.

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The invention provides a pharmaceutical composition described herein for use in treating or preventing haemorrhage in a subject. The invention provides a method for treating or preventing haemorrhage in a subject, the method comprising administering to the subject a pharmaceutical composition described herein. The invention provides a use of a pharmaceutical composition described herein in the manufacture of a medicament for the treatment or prevention of haemorrhage in a subject.

The pharmaceutical composition may be administered parenterally to the subject, preferably intramuscularly to the subject. The pharmaceutical composition may be administered intramuscularly to the subject *via* the deltoid, dorsogluteal, ventrogluteal, rectus femoris or vastus lateralis.

The amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject may be a therapeutically effective amount.

The amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject may be within about a 25%, 20%, 15%, 10% or 5% range around 6.36 mmol, preferably within about a 10% range around 6.36 mmol, more preferably within about a 5% range around 6.36 mmol. Thus, the amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject may be about 4.77 mmol to about 7.95 mmol, about 5.09 mmol to about 7.63 mmol, 5.41 mmol to about 7.31 mmol, 5.72 mmol to about 7.00 mmol, 6.04 mmol to about 6.68 mmol.

The amount of TXA administered to the subject may be within about a 25%, 20%, 15%, 10% or 5% range around 1g, preferably within about a 10% range around 1g, more preferably within about a 10% range around 1g. Thus, the amount of TXA administered to the subject may be about 0.75 g to about 1.25 g, about 0.8 g to about 1.2 g, about 0.85 g to about 1.15 g, about 0.9 g to about 1.1 g or about 0.95 g to about 1.05 g, preferably about 0.9 g to about 1.1 g. The amount of TXA administered to the subject may be 1g.

The pharmaceutical composition may be administered to the subject in a single dose. Preferably, the pharmaceutical composition is administered intramuscularly in a single dose.

The volume of pharmaceutical composition administered may be no more than about 5 mL in total, no more than about 4 mL in total, no more than about 3 mL in total, or about 2 to about 3 mL in total, or about 2 to about 2.5 mL in total, preferably about 2 to about 2.5 mL in total, more preferably about 2.2 mL in total.

5

The subject may not have been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24, 18, 12, 6, 4, 3, or 2 hours or in the previous 90, 60 or 30 minutes. Preferably, the subject has not been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24 hours.

10

The pharmaceutical composition may be administered to the subject within 15, 30, 60 or 90 minutes; or within 2, 3, 4, 8, 12 or 24 hours of an event that has caused or may cause haemorrhage. Preferably, the pharmaceutical composition is administered to the subject within 3 hours of an event that has caused or may cause haemorrhage. More preferably, the pharmaceutical composition is administered to the subject within 60 minutes of an event that has caused or may cause haemorrhage.

15

The term "haemorrhage" as used herein refers to an acute loss of blood and may be caused by a traumatic injury, surgery, medical condition or infectious disease.

20

Traumatic injuries that may cause haemorrhage includes abrasions, excoriations, hematomas, lacerations, incisions, puncture wounds, contusions, crushing and ballistic trauma. Medical conditions that may cause haemorrhage are causes which are not directly due to trauma and include haemorrhage due to intravascular changes (e.g. increase in blood pressure, decrease in clotting factors), intramural changes (e.g. aneurysms, dissections, AVMs, vasculitides) and extravascular changes (e.g. H pylori infection, brain abscess, brain tumor). Infectious diseases that may cause haemorrhage include Ebola, Marburg virus disease and yellow fever.

25

30

Subjects may experience haemorrhage due to surgery, trauma, or other forms of tissue damage; coagulopathy, including coagulopathy in multi-transfused subjects; congenital or acquired coagulation or bleeding disorders, including decreased liver function, defective platelet function or decreased platelet number; lacking or abnormal essential clotting molecules (e.g., platelets or von Willebrand factor protein); increased fibrinolysis;

- anticoagulant therapy or thrombolytic therapy; stem cell transplantation. Haemorrhage may occur in organs such as the brain, inner ear region, eyes, liver, lung, tumour tissue, gastrointestinal tract and uterus. Haemorrhage may occur in connection with surgery or trauma in subjects having acute hemarthrosis (bleedings in joints), chronic haemophilic
- 5 arthropathy, haematomas, (e.g., muscular, retroperitoneal, sublingual and retropharyngeal), bleedings in other tissue, haematuria (bleeding from the renal tract), cerebral haemorrhage, surgery (e.g., hepatectomy), dental extraction, and gastrointestinal bleedings (e.g., UGI bleeds).
- 10 Thus, the disease or disorder may be coagulopathy, including coagulopathy in multi-transfused subjects, congenital or acquired coagulation or bleeding disorders, including decreased liver function, defective platelet function or decreased platelet number, acute hemarthrosis (bleedings in joints), chronic haemophilic arthropathy, haematomas (e.g., muscular, retroperitoneal, sublingual and retropharyngeal), bleedings in other tissue,
- 15 haematuria (bleeding from the renal tract), cerebral haemorrhage, Ebola, Marburg virus disease, yellow fever, increase in blood pressure, decrease in clotting factors, intramural changes (e.g. aneurysms, dissections, AVMs, vasculitides), extravascular changes (e.g. H pylori infection, brain abscess, brain tumor), heavy menstrual bleeding, post-operative bleeding, hemophilia, cancer (e.g. breast and prostate cancer), stroke, traumatic brain injury,
- 20 postpartum haemorrhage, epistaxis and/or acute respiratory distress syndrome.

The pharmaceutical composition may be administered to the subject outside of a clinical setting. Thus, in certain embodiments the pharmaceutical composition is not administered to the subject in a hospital or clinic. The pharmaceutical composition may be administered to

25 the subject prior to the subject being transferred to hospital. After a pharmaceutical composition described herein has been administered to the subject, the subject may receive one or more further doses of TXA or a pharmaceutically acceptable salt thereof. The one or more further doses of TXA or a pharmaceutically acceptable salt thereof may be administered in a clinical setting (such as a hospital or clinic). The further one or more doses

30 of TXA or a pharmaceutically acceptable salt thereof may be administered intravenously, orally or intramuscularly, optionally intravenously or orally. A further dose of TXA or a pharmaceutically acceptable salt thereof may be administered at least 6 or at least 8 hours after administering the pharmaceutical composition described herein. The subject may receive a maximum dose of 19.1 mmol TXA or a pharmaceutically acceptable salt thereof in

a 24-hour period. Thus, the subject may receive a maximum dose of 3g TXA in a 24-hour period.

Devices

- 5 All aspects and embodiments described in relation to the other aspects of the invention (in particular the pharmaceutical compositions and medical uses) apply *mutatis mutandis* to the related containers and injection devices described below.

The invention provides a container containing one dose or a plurality of doses of the pharmaceutical composition or pharmaceutical composition for use described herein.

- 10 Preferably, the container provides one dose of the pharmaceutical composition or pharmaceutical composition for use described herein.

The amount of TXA or a pharmaceutically acceptable salt thereof in a dose may be within about a 10% or 5% range around 6.36 mmol. The amount of TXA in a dose may be within about a 10% or 5% range around 1g. The amount of TXA in a dose may be 1g.

- 15 The container may be an ampoule, vial, bottle or cartridge. The container may not interact physically or chemically with the composition stored within the container. The container may be composed of materials that allow inspection of the contents. Containers may be closed or sealed to prevent contamination or loss of contents. The container may protect the composition when exposed to anticipated extreme conditions of manufacturing, storage, shipment, and distribution. The container may comprise glass or plastic. Preferably, the
20 container is a glass container. Glass may include EP Type I, EP Type II or EP Type III glass. Preferably, the glass is EP Type I. The glass may be clear or amber. Plastics may include polyethylene, polyvinylchloride, polypropylene, polyamide (Nylon), polycarbonate, ethylene vinyl acetate and mixtures thereof.

- 25 The invention also provides an injection device for single or multiple use, wherein the injection device comprises an injection needle and a container described herein.

The injection needle may comprise stainless steel or plastic. The length of the injection needle may range from ¼ inch to 6 inch. The gauge of the injection needle may range from 11 to 32 G. The shape of the injection needle may be regular, short bevel, intradermal or
30 winged. Preferably, the injection needle is 1-3 inches in length and has a gauge of 19-25 G.

The container may be a cartridge for an autoinjector device or a pre-filled syringe. The injection device may be an autoinjector or pre-filled syringe. An autoinjector may be driven by a spring system and enclose a pre-filled syringe or cartridge. A number of auto injectors are commercially available including AutoJect 2, Betaject Light, Rebiject II, SimpleJect, 5 MiniJect, EpiPen, Vai and YpsoMate 2.25. The injection device may be single or multiple use.

Preparatory methods

All aspects and embodiments described in relation to the other aspects of the invention (in particular the pharmaceutical compositions, medical uses and devices) apply *mutatis* 10 *mutandis* to the related preparatory methods described below.

The invention provides a method of preparing a composition described herein, wherein the method comprises:

- (a) providing an aqueous acid solution; and
- 15 (b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid solution.

The method may further comprise adding concentrated acid, further aqueous acid solution and/or water. The amount of concentrated acid, further aqueous acid solution and/or water 20 may be added to adjust the pH and/or concentration of TXA or pharmaceutically acceptable salt thereof. Concentrated acid refers to acid which is at least 25%, at least 30%, at least 37%, at least 50%, at least 75%, at least 90% by mass, preferably at least 37% by mass acid. The TXA or a pharmaceutically acceptable salt thereof added to the aqueous acid solution may be solid. The method may also further comprise adding one or more bases as 25 described herein (such as sodium hydroxide) to adjust the pH of the composition to a pH as described herein. The one or more bases may comprise solid or an aqueous solution.

The aqueous acid solution in step (a) may be about 1N to about 9N, about 2N to about 8N, about 3N to about 7N, about 4N to about 6N, about 4N to about 5N, preferably about 4N to 30 about 6N, more preferably about 4N to about 5N. The aqueous acid solution may comprise any of the acids described herein. Preferably, the acid is an inorganic acid such as hydrochloric acid. Thus, the aqueous acid solution in step (a) may be a 4N, 5N, or 6N

inorganic acid, preferably 4N or 5N inorganic acid. The aqueous acid solution in step (a) may be 4N, 5N, or 6N hydrochloric acid, preferably 4N or 5N hydrochloric acid.

- 5 When the aqueous acid solution is about 4N, concentrated acid (such as at least 37% by mass acid) may be added to adjust the pH and/or concentration of TXA or pharmaceutically acceptable salt thereof. When the aqueous acid solution is about 5N, further aqueous acid solution and/or water may be added to adjust the pH and/or concentration of TXA or pharmaceutically acceptable salt thereof.
- 10 The method may further comprise at least one filtration step, preferably, the method comprises a first filtration step after the TXA has been dissolved in acidic solution. The method may comprise a second filtration step performed on the final solution. Filtering the solution after TXA dissolves in acidic solution provides a clear solution which may optimise the overall preparation process.
- 15 In some embodiments, the invention provides a method of preparing a composition described herein, wherein the method comprises:
- (a) providing an aqueous acid solution,
 - (b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid
 - 20 solution to dissolve TXA,
 - (c) pH adjustment of the solution as needed until a pH of about 4 is reached,
 - (d) adding WFI as needed to make up the solution to the final volume, and
 - (e) preferably filtering the final solution.
- 25 In some embodiments, the invention provides a method of preparing a composition described herein, wherein the method comprises:
- (a) providing an aqueous acid solution,
 - (b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid
 - solution to dissolve the TXA,
 - 30 (c) filtering the solution to obtain a clear solution,
 - (d) pH adjustment of the solution as needed until a pH of about 4 is reached,
 - (e) adding WFI as needed to make up the solution to the final volume, and
 - (f) filtering the final solution.

The aqueous acid solution in step (a) is preferably 4N HCl. It has been observed that an approximate acid:TXA ratio of 1.1:1 - 1.3:1 by mass, preferably around 1.2:1, is suitable for fully dissolving the TXA and for achieving the desired pH. This may obviate the need for further pH adjustment, thereby simplifying the process.

5

pH adjustment, if needed, according to these methods typically comprises adding acid (in order to decrease pH) but may comprise adding base (in order to increase pH) as needed.

Dissolving the TXA is preferably facilitated by mixing (e.g. vortexing). Heating is not required.

10

The invention provides a method of preparing a composition described herein, wherein the method comprises:

(a) providing an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof, and

15

(b) adding acid until the pH of the solution reaches about 3 to about 5, preferably about 4.

The invention provides a composition prepared by any of the methods described herein.

20

The invention also provides a method of preparing a container described herein, wherein the method comprises:

(a) sterilising an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof; and

(b) adding the sterilised solution comprising TXA or a pharmaceutically acceptable salt thereof to a container.

25

The container in step (b) is preferably sterilised.

The invention also provides a method of preparing a container described herein, wherein the method comprises:

30

(a) adding an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof to a container; and

(b) sterilising the container with the aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof comprised therein.

The invention provides a container prepared by any of the methods described herein.

5 The container with the pharmaceutical composition comprised therein may be sterilized either by terminal sterilisation or by filtration, followed by aseptic processing. Terminal sterilisation is when the pharmaceutical composition is sterilised after being added to the container. Terminal sterilisation may be achieved by applying heat or radiation to the container with the pharmaceutical composition added.

10 The compositions may be terminally sterilized using moist heat. Terminal sterilization can be used to destroy all viable microorganisms within the final, sealed container containing the pharmaceutical composition. An autoclave is typically used to accomplish terminal heat-sterilization of drug products in their final packaging. Typical autoclave cycles in the pharmaceutical industry to achieve terminal sterilization of the final product are 121 °C for at
15 least 10 minutes.

Aseptic processing is when the pharmaceutical composition and container are separately sterilised with the pharmaceutical composition then added to the container under aseptic conditions with no terminal sterilization step after the pharmaceutical composition is added
20 to the container. The pharmaceutical composition may be sterilised by filtration for example by use of particle filters, microfilters, ultrafilter and/or nanofilters. The pharmaceutical composition may be sterilised by heat or radiation. The container may be sterile as a result of its manufacture or by any means known in the art. The pharmaceutical composition may be sterilised before being added to the container and sterilised in the container. Known
25 means of sterilisation include heat sterilisation, gas sterilisation, radiation sterilisation, light sterilisation, and filtration.

Procedures for filling pharmaceutical compositions in pharmaceutically acceptable containers, and their subsequent processing are known in the art. These procedures can be
30 used to produce sterile pharmaceutical drug products often required for health care. See, e.g., Akers, M.J. (2010). Sterile Drug Products: Formulation, Packaging, Manufacturing and Quality (1st ed.). CRC Press. <https://doi.org/10.3109/9781420020564>. Examples of suitable procedures for producing sterile pharmaceutical drug products include, but are not limited to, terminal moist heat sterilization, ethylene oxide, radiation (i.e., gamma and electron beam),

and aseptic processing techniques. Any one or more of these sterilization procedures can be used to sterilize the pharmaceutical compositions described herein.

Definitions

5

The term “about,” as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature, and the like, is meant to encompass variations within the error of measurement for the specified amount.

10 The terms “comprises” and/or “comprising,” when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof.

15 The term “pharmaceutical composition” refers to a composition that is suitable for therapeutic use and, thus, has certain properties known to one of skill in the art.

The term “therapeutically effective amount” refers to the amount of a compound that, when administered to a subject for treating a disease or condition, is sufficient to effect such
20 treatment to fully or substantially alleviate the symptoms of the disease state or condition. The “therapeutically effective amount” can vary depending on the compound, the disease and its severity, and the condition, age, weight, gender etc. of the subject to be treated.

A therapeutically effective amount of TXA or pharmaceutically acceptable salt thereof may
25 be the amount sufficient to prevent or alleviate haemorrhage before, during and/or after an event that has or may cause haemorrhage.

The terms “treating” and “treatment” of a disease state or condition include: (i) preventing the disease state or condition, i.e., causing the clinical symptoms of the disease state or condition
30 not to develop in a subject that may be exposed to or predisposed to the disease state or condition, but does not yet experience or display symptoms of the disease state or condition, (ii) inhibiting the disease state or condition, i.e., arresting the development of the disease state or condition or its clinical symptoms, or (iii) relieving the disease state or condition, i.e., causing temporary or permanent regression of the disease state or condition or its clinical

symptoms. The terms "treating" or "treatment" may refer to the prevention or alleviation of haemorrhage.

5 The terms, "patient", "subject" or "subjects" include but are not limited to humans, the term may also encompass other mammals, or domestic or exotic animals, for example, dogs, cats, ferrets, rabbits, pigs, horses, cattle, birds, or reptiles.

10 Tranexamic acid, also known as *trans*-4-(aminomethyl) cyclohexanecarboxylic acid, also referred to as TXA, for example having CAS RN: 1197-18-8, is an antifibrinolytic hemostatic agent used to prevent or treat severe haemorrhage. Tranexamic acid may be synthesised by any means known in the art (see e.g. WO2015104721A2, US3923879, US4048222A and WO202111475A1, all of which are incorporated herein by reference).

15 The term "pharmaceutically acceptable salt" includes for example and without limitation the sodium salt, potassium salt, lithium salt, calcium salt, magnesium salt and the like; as well as the hydrochloride, hydrobromide, sulfate, phosphate, formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonatemethanesulfonate salt forms, and the like. Preferably, the active ingredient for use in accordance with the present invention is tranexamic acid.

20 The term "aqueous pharmaceutical composition", as used herein, refers to a composition suitable for therapeutic use in which the aqueous component comprises water, preferably distilled water, deionized water, water for injection, sterile water for injection or bacteriostatic water for injection.

25 Unless otherwise defined, 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 disclosure belongs. In the event of conflicting terminology, the present specification is controlling.

30 **DESCRIPTION OF THE FIGURES**

These and other aspects of the invention will now be described with reference to the accompanying Figures, in which:

Figure 1A is an image showing the appearance of Formulation C after its preparation at ambient temperature (18-25°C). A clear solution can be observed.

Figure 1B is an image showing the appearance of Formulation C after it has been refrigerated overnight at 2-8°C. Precipitation in the form of crystalline material can be observed.

Figure 2A is an image showing the appearance of Formulation D after its preparation at ambient temperature (18-25°C). A clear solution can be observed.

Figure 2B is an image showing the appearance of Formulation D after it has been refrigerated overnight at 2-8°C. A clear solution can be observed.

EXAMPLES

The invention will be further appreciated with respect to the following non-limiting examples. Other variations or embodiments of the invention will also be apparent to one of ordinary skill in the art from the above descriptions and examples. Thus, the foregoing embodiments are not to be construed as limiting the scope of this invention.

ABBREVIATIONS

ACN	:	Acetonitrile
ACS	:	American Chemical Society
AD	:	Analytical Development
25 API	:	Active Pharmaceutical Ingredient
BB	:	Blow Back
BP	:	British Pharmacopoeia
ChP	:	Chinese Pharmacopoeia
DP	:	Drug Product
30 EP	:	European Pharmacopoeia
FCC	:	Food Chemicals Codex
FD	:	Formulation Development
HPLC	:	High-performance liquid chromatography
IR	:	Infra-Red

- JP : Japanese Pharmacopoeia
- NA : Not Applicable
- NAP : Not Applicable
- NF : National Formulary
- 5 PDS : Pharmaceutical development services
- PEG : Polyethylene glycol
- PPE : Personal Protective Equipment
- PTFE : Polytetrafluoroethylene
- PVDF : Polyvinylidene Fluoride
- 10 SST : System Suitability Test
- TXA : Tranexamic acid
- USP : United States Pharmacopoeia
- UV : Ultraviolet
- WFI : Water for injection

15

MATERIALS AND METHODS

The details of primary packaging materials used for DP preparation are captured in Table 1.

20

Table 1: Details of the primary packaging materials

Description
Nuova Ompi, ISO 2R vials with ESBB feature – presterilized
13 mm, 1358 4023/50/GREY, B2-40 (FLUROTEC coated)
13 mm White Flip-off seals

The details of excipients used for the screening of different buffer systems and solubility enhancers are captured in Table 2.

25

Table 2: Details of excipients used

Excipient Name	Supplier	Grade
Sodium acetate trihydrate	Merck	EP, BP, ChP ,JP, USP
Glacial Acetic Acid	Merck	EP, BP, JP, USP, E260

Excipient Name	Supplier	Grade
Sodium monobasic phosphate dihydrate	Merck	EP, BP, USP, JPE
Di-sodium hydrogen phosphate	Merck	EP, BP, USP, JPE, E 339
Citric acid	Merck	EP, BP, ChP, JP, USP, E 330, FCC
Tri-sodium citrate dihydrate	Merck	EP, BP, JP, USP, E 331
Sodium Chloride	Merck	EP, BP, JP, USP
Sodium hydroxide pellets	Merck	EP, BP, JP, NF
Hydrochloric acid	Merck	EP, BP, JP, NF
Glycerol/Glycerin	Merck	EP, BP, JP, USP, ACS
1,2-Propanediol (1,2-Propylene glycol)	Merck	EP, BP, USP
Polyethylene glycol 300	Merck	EP
Captisol (Sulfobutyl betadex sodium)	Sigma-Aldrich	JP, EP, USP-NF
Kolliphor EL (Polyoxyl-35 castor oil)	Sigma-Aldrich	NAP

The list of equipment used for this study is captured in Table 3.

Table 3: List of Equipment

5

Equipment	Manufacturer
Glassware	Schott / Duran
PTFE-coated magnetic stir bars	Carlo Erba
PVDF	PALL
ISO2R vials	NuovaOmpi
Magnetic stirrer	Heidolph
Analytical balance (25 mg to 200 g)	Mettler Toledo
Technical balance (30 g to 8.0 Kg)	Mettler Toledo
pH meter	Mettler Toledo
Digital timer	Heraeus
Peristaltic pump for filtration operation	Watson Marlow

Autoclave, mod. FOB5C-TS	Fedegari
Refrigerators or freezers	Angelantoni / ThermoFisher
IR thermometer	Dostmann Electronic
HPLC with UV/PDA detector	Waters
4.8mm Pt-cured silicon tubing	WATSON-MARLOW SRL
Osmometer	Advanced Instruments
Digital density-meter	Mettler Toledo

Analytical data generated in support of the initial stages of the formulation development work were produced using a preliminary, fit for use HPLC method which was still undergoing optimization. Analytical data generated in support of the later stages of the formulation development work were produced using a final optimized HPLC method. Hence, parameters for both analytical methods are presented below as Method A and Method B.

Method A (preliminary HPLC method)

The parameters of the preliminary HPLC method are presented below:

- 10 • Mobile phase A (85% Buffer A:15% ACN)
 - Buffer A in water:
 - 10.5 g/L $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (Sodium Phosphate Buffer)
 - 8 mL/L Triethylamine
 - 2.3 g/L Sodium Dodecyl Sulphate
 - 15 ○ pH adjusted to 2.5 with H_3PO_4 (85%)
- Column: Zorbax Eclipse XDB-C18 5 μm , 4.6 x 250 mm (P/N:990967-902)
- Flow 1.0 mL/min
- Column temperature: 40°C
- 20 • Carousel temperature: 5 – 10 °C
- Wavelength: 210 nm
- Sample concentration:
 - 1.0 mg/mL in water (Assay and SST) and
 - 10 mg/mL in water (for related substances)
- 25 • Injection volume: 20 μL
- Run Time:

- 30 minutes for assay
- 60 minutes for related substances
- Needle wash: Water/ACN (50:50)

5 Method B (finalized HPLC method parameters)

The parameters of the finalized HPLC method are presented below:

- Mobile phase A (85% Buffer A:15% ACN)
 - Buffer A in water:
 - 10.5 g/L $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (Sodium Phosphate Buffer)
 - 8 mL/L Triethylamine
 - 2.3 g/L Sodium Dodecyl Sulphate
 - pH adjusted to 2.5 with H_3PO_4 (85%)
- Column: Zorbax Eclipse XDB-C18 5 μm , 4.6 x 250 mm (P/N:990967-902)
- Flow 1.0 mL/min
- Column temperature: 55°C
- Carousel temperature: 5 – 10 °C
- Wavelength: 210 nm
- Sample concentration:
 - 1.0 mg/mL in mobile phase A (Assay and SST) and
 - 10 mg/mL in mobile phase A (for related substances)
- Injection volume: 20 μL
- Run Time:
 - 30 minutes for assay
 - 60 minutes for related substances
- Needle wash: Water/ACN (50:50)

EXAMPLE 1

30 1.1 Buffer systems screening and pH dependent solubility

Buffer system (pH, buffer type and buffer strength) screening was combined with the assessment of pH dependent solubility (to understand the solubility of TXA at different pH conditions) and to select the right buffer system considering the solubility and stability. Hence, an excess quantity of TXA was added to each formulation buffer during the

dissolution step. At the end of the mixing time (approximately 2 hours) the solutions were filtered, filled into vials, and a stability study initiated.

Each DP was prepared by the following 2 steps:

- 5
- 1) Preparation of the target buffer system for each formulation

2) Addition of excess quantity of API to each DP specific buffer system followed by mixing for 2 hours to enable the dissolution of TA, filtration, filling into the vials.

1.2 Target formulation buffer preparation

- 10
- The following formulation buffers were prepared:
1. Formulation buffer 1: 20 mM acetate buffer with target pH of 4.0

2. Formulation buffer 2: 20 mM phosphate buffer with target pH of 6.0

3. Formulation buffer 3: 20 mM phosphate buffer with target pH of 7.0

4. Formulation buffer 4: 50 mM phosphate buffer with target pH of 7.0

15

5. Formulation buffer 5: 20 mM phosphate buffer with target pH of 10.0

6. Formulation buffer 6: 20 mM citrate buffer with target pH of 6.0

7. Formulation buffer 7: 20 mM citrate buffer with target pH of 7.0

1.3 DP Preparation

20 1.3.1 DP/Formulation 1 Preparation

Formulation 1 was prepared by following the steps described below:

- Glass bottle (500 mL) was taken and labelled as Formulation 1.

• 200 mL of formulation buffer 1 (20 mM acetate buffer with target pH of 4.0) was added to the labelled glass bottle containing the magnetic stir bar.

25

• The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.1 below:

Table 1.1: Preparation of Formulation 1

Step Description	Value/ Data	Notes
Volume of formulation buffer 1 taken	200 mL	pH of formulation buffer 1 is 4.0 at 24.1°C
Amount of TXA added (under continuous stirring)	59.60 g	NA

pH/temperature (°C) after mixing for approx. 10 minutes	6.41/25°C	Undissolved TXA was present
Volume of 5N HCl added for pH adjustment	53.0 mL	TXA is completely dissolved while adjusting the pH
Amount of TXA added (under continuous stirring)	19.97 g	NA
pH/temperature (°C)	4.48/25°C	White and opalescent solution was obtained with undissolved TXA
Volume of 5N HCl added for pH adjustment	19 mL	TXA is completely dissolved while adjusting the pH
pH/temperature (°C)	4.01/26°C	NA
Amount of TXA added (under continuous stirring)	30.04 g	NA
pH/temperature (°C)	4.39/25°C	White and opalescent solution was obtained with undissolved TXA
Volume of 5N HCl added for pH adjustment	24 mL	TXA is completely dissolved while adjusting the pH
pH/temperature (°C)	4.04/26°C	NA
Amount of TXA added (under continuous stirring)	20.02 g	NA
pH/temperature (°C)	4.23/26°C	White and opalescent solution was obtained with undissolved TA
Volume of 5N HCl added for pH adjustment	19 mL	TXA is completely dissolved while adjusting the pH
pH/temperature (°C)	4.03/26°C	NA
Density	1.0706 g/mL	NA

- The pH adjustment has taken a greater volume of 5N HCl during the pH adjustment and it has consequently diluted the concentration of TXA. Hence TXA addition was not continued further though a clear solution was obtained after the last pH adjustment described above in Table 1.1.
- The solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
- The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

1.3.2 DP/Formulation 2 Preparation

Formulation 2 was prepared by following the steps described below:

- 500 mL glass bottle was taken and labelled as Formulation 2.

- 200 mL of formulation buffer 2 (20 mM phosphate buffer with target pH of 6.0) was added to the labelled glass bottle containing the magnetic stir bar.
- The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.2 below:

5

Table 1.2: Preparation of Formulation 2

Step Description	Value/ Data	Notes
Volume of formulation buffer 2 taken	200 mL	pH of formulation buffer 2 is 6.0 at 25.2°C
Amount of TXA added (under continuous stirring)	60.01 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	6.73/25°C	Undissolved TXA was present
Volume of 1N HCl added for pH adjustment to the target pH value (6.0)	8.3 mL	NA
pH/temperature (°C)	6.02/25°C	White and opalescent solution was obtained with undissolved TA
Final pH/temperature (°C) after mixing the solution for 60 minutes	6.02/25°C	Undissolved TXA was present

- After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
- The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

10

1.3.3 DP/Formulation 3 Preparation

Formulation 3 was prepared by following the steps described below:

- 500 mL glass bottle was taken and labelled as Formulation 3.
- 200 mL of formulation buffer 3 (20 mM phosphate buffer with target pH of 7.0) was added to the labelled glass bottle containing the magnetic stir bar.
- The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.3 below:

15

20

Table 1.3: Preparation of Formulation 3

Step Description	Value/ Data	Notes
Volume of formulation buffer 3 taken	200 mL	pH of formulation buffer 3 is 7.0 at 25.0°C
Amount of TXA added (under continuous stirring)	59.96 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	7.10/25°C	Undissolved TXA was present
Volume of 1N HCl added for pH adjustment to the target pH value (7.0)	0.3 mL	NA
pH/temperature (°C)	7.00/25.0°C	White and opalescent solution was obtained with undissolved TA
Final pH/temperature (°C) after mixing the solution for 60 minutes	6.98/25.0°C	Undissolved TXA was present

- 5
- After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
 - The filtered DP solution was manually filled into the 2R vials (fill volume – 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

1.3.4 DP/Formulation 4 Preparation

- 10
- Formulation 4 was prepared by following the steps described below:
- 500 mL glass bottle was taken and labelled as Formulation 4.
 - 200 mL of formulation buffer 4 (50 mM phosphate buffer with target pH of 7.0) was added to the labelled glass bottle containing the magnetic stir bar.
- 15
- The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.4 below:

Table 1.4: Preparation of Formulation 4

Step Description	Value/ Data	Notes
Volume of formulation buffer 4 taken	200 mL	pH of formulation buffer 4 is 7.04 at 23.3°C
Amount of TXA added (under continuous stirring)	59.99 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	7.00/25°C	White and opalescent solution was obtained with undissolved TA
Final pH/temperature (°C) after mixing the solution for 60 minutes	6.99/25.0°C	Undissolved TXA was present

- After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
- The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

1.3.5 DP/Formulation 5 Preparation

Formulation 5 was prepared by following the steps described below:

- 10
- 500 mL glass bottle was taken and labelled as Formulation 5.
 - 200 mL of formulation buffer 5 (20 mM phosphate buffer with target pH of 10.0) was added to the labelled glass bottle containing the magnetic stir bar.
 - The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.5 below:

15 **Table 1.5: Preparation of Formulation 5**

Step Description	Value/ Data	Notes
Volume of formulation buffer 5 taken	200 mL	pH of formulation buffer 5 is 9.99 at 25.0°C
Amount of TXA added (under continuous stirring)	60.01 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	7.92/24.7°C	White and opalescent solution was obtained with undissolved TA
Volume of 4N NaOH added for pH adjustment to the target pH value (10.0)	9.4 mL	NA
pH/temperature (°C)	9.96/25.0°C	White and opalescent solution was obtained with undissolved TA
Final pH/temperature (°C) after mixing the solution for 60 minutes	9.98/25.0°C	Undissolved TXA was present

- | | |
|--|---|
| | <ul style="list-style-type: none"> • After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling. • The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability. |
|--|---|

1.3.6 DP/Formulation 6 Preparation

Formulation 6 was prepared by following the steps described below:

- 500 mL glass bottle was taken and labelled as Formulation 6.
- 200 mL of formulation buffer 6 (20 mM citrate buffer with target pH of 6.0) was added to the labelled glass bottle containing the magnetic stir bar.
- 5 • The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.6 below:

Table 1.6: Preparation of Formulation 6

Step Description	Value/ Data	Notes
Volume of formulation buffer 6 taken	200 mL	pH of formulation buffer 6 is 6.01 at 24.0°C
Amount of TXA added (under continuous stirring)	60.00 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	6.78/25.0°C	White and opalescent solution was obtained with undissolved TXA
Volume of 1N HCl added for pH adjustment to the target pH value (6.0)	8.6 mL	NA
pH/temperature (°C)	6.01/25.0°C	White and opalescent solution was obtained with undissolved TXA
Final pH/temperature (°C) after mixing the solution for 60 minutes	6.02/25.0°C	Undissolved TXA was present

- After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
- 10 • The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

15

1.3.7 DP/Formulation 7 Preparation

Formulation 7 was prepared by following the steps described below:

- 500 mL glass bottle was taken and labelled as Formulation 7.
- 200 mL of formulation buffer 7 (20 mM citrate buffer with target pH of 7.0) was added to the labelled glass bottle containing the magnetic stir bar.
- 20 • The steps followed during the addition of the API followed by the adjustment of pH are described in Table 1.7 below:

Table 1.7: Preparation of Formulation 7

Step Description	Value/ Data	Notes
Volume of formulation buffer 7 taken	200 mL	pH of formulation buffer 7 is 7.01 at 24.3°C
Amount of TXA added (under continuous stirring)	60.06 g	NA
pH/temperature (°C) after mixing for approx. 10 minutes	7.46/25.0°C	White and opalescent solution was obtained with undissolved TXA
Volume of 1N HCl added for pH adjustment to the target pH value (7.0)	0.75 mL	NA
pH/temperature (°C)	7.00/25.0°C	White and opalescent solution was obtained with undissolved TXA
Final pH/temperature (°C) after mixing the solution for 60 minutes	7.02/25.0°C	Undissolved TXA was present

- 5
- After mixing for 60 minutes, the solution was filtered using a PVDF filter and 4.8 mm tubing into a sterile clean glass bottle. 10 mL of the initial filtrate was discarded prior to the collection of the filtrate into the glass bottle for filling.
 - The filtered DP solution was manually filled into the 2R vials (fill volume - 2 mL). The filled vials were stoppered, crimped, labelled, and placed on stability.

1.3.8 Development stability study on trial buffer systems

- 10
- The DP vials from all seven formulations were placed on a development stability study under real-time (25°C ± 2°C /60% RH ± 5% RH) and accelerated (40°C ± 2°C /75% RH ± 5% RH) conditions. The development stability study lasted for a total duration of 3 months. The details of the stability conditions and time points used in the study are presented in Table 1.8 below.

15

Table 1.8: Details for the stability study

Stability Condition	T0	1M	2M	3M
40°C ± 2°C / 75% RH ± 5% RH	X	X	X	X
25°C ± 2°C / 60% RH ± 5% RH		X	X	X

X – tested timepoints

The list of analytical methods used for the T0 (release) and for each time point analysis are mentioned below:

- 5
- General appearance of the solution against white and black backgrounds (no specific method available)
 - pH
 - Osmolality
 - Assay and Purity (see Section 1.1.3.1)

1.4 Results

10

1.4.1 pH

The pH data for all seven formulations over the stability duration of 3 months under long term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions are presented in Table 1.9 and Table 1.10 respectively.

15

No significant trends were observed in the pH data over the stability duration of 3 months under both long term and accelerated stability conditions, and data were within ± 0.2 units of the target pH value of each respective formulation.

Table 1.9: pH data under long term conditions (25°C/60% RH)

Formulation number	T0	T1M 25°C	T2M 25°C	T3M 25°C
Formulation 1	3.96 at 24.6°C	4.02 at 23.9°C	3.98 at 23.5°C	3.80 at 23.5°C
Formulation 2	6.02 at 24.4°C	6.04 at 23.8°C	6.05 at 23°C	6.01 at 23.1°C
Formulation 3	6.99 at 24.7°C	6.99 at 23.9°C	7.01 at 23.2°C	6.97 at 23.6°C
Formulation 4	6.99 at 24.7°C	6.99 at 23.3°C	7.02 at 23.1°C	6.98 at 23.7°C
Formulation 5	10.03 at 24.6°C	10.05 at 23.5°C	10.08 at 23.5°C	10.07 at 23.4°C
Formulation 6	6.00 at 24.6°C	6.01 at 23.6°C	6.02 at 23.6°C	6.00 at 23.2°C
Formulation 7	7.01 at 24.5°C	7.02 at 23.5°C	7.03 at 23.5°C	7.02 at 23.1°C

Table 1.10: pH data under accelerated conditions (40°C/75% RH)

20

Formulation number	T0	T1M 40°C	T2M 40°C	T3M 40°C
Formulation 1	3.96 at 24.6°C	3.85 at 23.4°C	3.90 at 23.1°C	3.99 at 23.4°C
Formulation 2	6.02 at 24.4°C	6.02 at 23.5°C	6.08 at 23.1°C	6.02 at 23.8°C
Formulation 3	6.99 at 24.7°C	6.99 at 23.5°C	7.01 at 23.1°C	6.97 at 23.8°C
Formulation 4	6.99 at 24.7°C	7.01 at 23.4°C	7.01 at 23.1°C	6.97 at 23.6°C
Formulation 5	10.03 at 24.6°C	10.09 at 23.3°C	10.10 at 23.1°C	10.06 at 23.1°C
Formulation 6	6.00 at 24.6°C	6.00 at 23.4°C	6.03 at 23.2°C	6.01 at 23.3°C
Formulation 7	7.01 at 24.5°C	7.04 at 23.4°C	7.06 at 23.2°C	7.03 at 23.2°C

1.4.2 Osmolality

The osmolality data for all seven formulations over the stability duration of 3 months under long term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions are presented in Table 1.11 and Table 1.12 respectively.

No significant trends were observed in the osmolality data over the stability duration of 3 months under both long term and accelerated stability conditions.

Table 1.11: Osmolality data under long term conditions (25°C/60% RH)

Formulation number	T0	T1M_25°C	T2M_25°C	T3M_25°C
Formulation 1	3042	3174	3117	3153
Formulation 2	1048	1267	1268	1271
Formulation 3	1019	976	961	949
Formulation 4	1102	1019	1053	1056
Formulation 5	1329	1200	1316	1357
Formulation 6	1009	1130	996	1028
Formulation 7	1033	1026	982	1035

Table 1.12: Osmolality data under accelerated conditions (40°C/75% RH)

Formulation number	T0	T1M_40°C	T2M_40°C	T3M_40°C
Formulation 1	3042	3084	3132	3171
Formulation 2	1048	1093	1050	1092
Formulation 3	1019	970	972	948
Formulation 4	1102	1041	963	1041
Formulation 5	1329	1381	1324	1384
Formulation 6	1009	1035	1097	1061
Formulation 7	1033	1039	990	997

1.4.3 Appearance

The appearances of all seven formulations over the stability duration of 3 months under long term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions are presented in Table 1.13 and Table 1.14 respectively.

No significant trends were observed in the appearance data over the stability duration of 3 months, except for formulation 5 at the T3M timepoint under accelerated conditions, where the colour was observed to have changed from colourless to light red. The solution also contained several large transparent particles. It is possible this was due to the high pH of this system (i.e., pH 10.0).

Table 1.13: Appearances under long term conditions (25°C/60% RH)

Formulation number	T0	T1M_25°C	T2M_25°C	T3M_25°C
Formulation 1	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 2	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 3	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 4	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 5	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 6	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 7	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution

Table 1.14: Appearances under accelerated conditions (40°C/75% RH)

Formulation number	T0	T1M_40°C and T2M_40°C	T3M_40°C
Formulation 1	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 2	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 3	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 4	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 5	Clear, non-opalescent solution	Clear, non-opalescent solution	Light red colour solution with several big transparent particles
Formulation 6	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution
Formulation 7	Clear, non-opalescent solution	Clear, non-opalescent solution	Clear, non-opalescent solution

5 1.4.4 Assay

The assay data for all seven formulations over the stability duration of 3 months under long term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions are presented in Table 1.15 and Table 1.16 respectively.

No significant trends were observed in the assay data over the stability duration of 3 months under both long term and accelerated stability conditions.

Formulation 1 at pH 4.0 clearly shows higher TXA solubility compared to the other pH conditions evaluated i.e., pH 6.0 (Formulation 2 and 6), pH 7.0 (Formulation 3, 4 and 7) and pH 10.0 (Formulation 5). The maximum solubility achieved at pH 6.0, pH 7.0 and pH 10.0 conditions was 160 mg/mL, 153 mg/mL and 168 mg/mL respectively.

These data demonstrate that pH 4.0 is likely to be the optimal pH for formulating the proposed DP at the required concentration of TXA.

Table 1.15: Assay data under long term conditions (25°C/60% RH)

Formulation number	Concentration (mg/mL)			
	T0	T1M	T2M	T3M
Formulation 1	309.4	309.3	333.4	330.4
Formulation 2	159.5	156.9	159.5	164.0
Formulation 3	153.2	151.4	152.3	155.9
Formulation 4	153.3	151.8	153.8	153.9
Formulation 5	167.8	165.4	167.6	170.7
Formulation 6	159.6	158.1	158.9	159.5
Formulation 7	151.8	150.8	152.4	156.7

Table 1.16: Assay data under accelerated conditions (40°C/75% RH)

Formulation number	Concentration (mg/mL)			
	T0	T1M	T2M	T3M
Formulation 1	309.4	307.2	307.1	307.8
Formulation 2	159.5	160.3	159.7	161.4
Formulation 3	153.2	154.5	152.4	154.8
Formulation 4	153.3	156.0	153.1	150.5
Formulation 5	167.8	171.0	167.7	175.4
Formulation 6	159.6	162.1	159.6	166.2
Formulation 7	151.8	154.7	152.8	154.1

1.4.5 Purity (chromatographic purity)

The purity data for all seven formulations over the stability duration of 3 months under long term (25°C/60% RH) and accelerated (40°C/75% RH) stability conditions are presented in Table 1.17 and Table 1.18 respectively.

No significant trends were observed in the purity data for formulation 1 (TXA in 20 mM acetate buffer with target pH of 4.0), formulation 3 (TXA in 20 mM phosphate buffer with target pH of 7.0), formulation 4 (TXA in 50 mM phosphate buffer with target pH of 7.0) and

formulation 7 (TXA in 20 mM citrate buffer with target pH of 7.0) over the stability duration of 3 months under both long term and accelerated stability conditions.

Formulation 7 at the T3M timepoint under the long-term condition showed a significant decrease in the purity result. This was considered as an out-of-trend result as no decrease in the purity was observed under the accelerated condition.

Table 1.17: Purity data under shelf-life conditions (25°C/60% RH)

Formulation number	Purity %			
	T0	T1M	T2M	T3M
Formulation 1	98.59	98.40	98.70	98.29
Formulation 2	98.61	98.69	98.78	98.85
Formulation 3	98.55	98.66	98.80	98.88
Formulation 4	98.59	98.62	98.67	98.78
Formulation 5	98.73	98.82	98.69	98.84
Formulation 6	98.61	98.76	98.80	96.17
Formulation 7	98.66	98.73	98.79	95.65

Table 1.18: Purity data under accelerated conditions (40°C/75% RH)

Formulation number	Purity %			
	T0	T1M	T2M	T3M
Formulation 1	98.59	98.39	98.67	98.58
Formulation 2	98.61	98.75	98.72	90.90
Formulation 3	98.55	98.72	98.65	98.78
Formulation 4	98.59	98.76	98.69	98.64
Formulation 5	98.73	98.68	98.41	97.94
Formulation 6	98.61	98.78	98.74	89.37
Formulation 7	98.66	98.58	98.75	98.77

- 10 In the case of formulation 2 (TXA in 20 mM phosphate buffer with target pH of 6.0), no significant trend was observed in the purity data under the long-term stability condition over 3 months. Under the accelerated stability condition, no significant trend was observed up to and including the 2 months timepoint. However, at 3 months, a significant drop in the purity was observed (98.6% to 90.9%).
- 15 In the case of formulation 6 (TXA in 20 mM citrate buffer with target pH of 6.0), no significant trend was observed in the purity data under both the long term and accelerated stability conditions, up to and including the 2 months timepoint. However, at the 3 months timepoint, a significant drop in the purity was observed under both the long-term condition (down to 96.2%) and the accelerated condition (down to 89.4%).

The long-term stability data generated on formulation 2 and formulation 6 would appear to demonstrate the impact of the buffer system used. Formulation 6, which utilised a citrate buffer system showed a reduction in purity under long term storage conditions, whereas formulation 2, which utilised a phosphate buffer system, showed no significant change in purity under the same storage conditions.

In the case of formulation 5 (TXA in 20 mM phosphate buffer with target pH of 10.0), no significant trend was observed in the purity data under the long-term stability condition over 3 months. However, under the accelerated stability condition, whilst no significant trend was observed up to and including the 2 months timepoint, at 3 months a decrease was observed (98.7% to 97.9%). In addition, the colour of the formulation had changed from colourless to a light red colour.

1.5 Conclusions

The data discussed above provides evidence that the solubility and stability of TXA is closely linked to pH. TXA has very high solubility (> 300 mg/mL) at pH 4.0 compared to the other pH conditions evaluated (i.e., pH 6.0, pH 7.0 and pH 10.0), where TXA solubility ranges from 150 to 170 mg/mL.

No significant differences were observed in the purity data of TXA at pH 4.0 and pH 7.0 over the stability duration of 3 months at both long term and accelerated stability conditions. In the case of pH 6.0, the purity of TXA was reduced at the 3-month timepoint under the accelerated stability condition. Additionally, formulation 5 with a target pH of 10.0, underwent a colour change under the accelerated stability condition.

Comparison of the stability data for formulation 2 (phosphate buffer) and formulation 6 (citrate buffer), which were both buffered at pH 6.0 with a buffer strength of 20 mM, demonstrated that TXA demonstrates better stability in phosphate buffer compared to citrate buffer. Formulation 6 utilising citrate buffer showed a reduction in purity under long term storage conditions, whereas formulation 2 utilising phosphate buffer showed no significant trend in purity over the duration of the development stability study.

EXAMPLE 2

2.1 Solubility enhancers screening

Different solubility enhancers (Propylene Glycol, PEG 300, Glycerol, Kolliphor EL and Captisol) were evaluated to select the right solubilizer for achieving a higher concentration

of TXA in solution. Initially the slurry API and WFI were prepared as detailed in Table 2.1 to Table 2.5.

To the slurry, increased quantities of each respective solubility enhancer was added until a clear solution was obtained. After each addition of solubility enhancer, the appearance of the solution was recorded. This approach was followed to evaluate the maximum solubility that could be achieved with each solubility enhancer and to compare the solubility data between the different solubility enhancers.

2.1.1 Glycerol

The steps followed while evaluating the solubility with glycerol are presented in Table 2.1.

Table 2.1: Solubility enhancement with glycerol

Step. No.	Component Added	Weight (g) added	Total cumulative amount (g)	Appearance of the solution
1	API	9.018	9.018	NAP
2	Water	4.922	13.939	Slurry was formed with undissolved TXA
3	Glycerol	2.001	15.940	White solution with undissolved TXA
4	Glycerol	2.062	18.002	White solution with undissolved TXA
5	Glycerol	2.011	20.013	White solution with undissolved TXA
6	Glycerol	1.995	22.008	White solution with undissolved TXA
7	Glycerol	3.014	25.022	White solution with undissolved TXA
8	Glycerol	3.003	28.025	White solution with undissolved TXA
9	Glycerol	3.025	31.050	White solution with undissolved TXA
10	Glycerol	3.004	34.054	White solution with undissolved TXA
11	Water	2.000	36.054	Water was added to increase the total mass of the sample
12	Glycerol	5.023	41.077	White solution with undissolved TXA
13	Glycerol	5.023	46.100	White solution with undissolved TXA
14	Glycerol	5.013	51.113	White solution with undissolved TXA
15	Glycerol	10.024	61.136	White solution with undissolved TXA
16	Glycerol	20.020	81.156	White solution with undissolved TXA
Final weight of the solution (g)			81.2 g	
Weight of solubilizer (Glycerol) in g			65.2 g	
Weight percent of solubilizer (%w/w)			80.4% w/w	

A clear solution was not achieved even after taking the glycerol content up to 80% of the final weight of the solution, which was 81.2 g. After the last addition, mixing of the solution

continued for approx. 30 minutes. The required volume (10 mL) of the solution was then filtered by using a PVDF syringe filter and tested for Assay.

2.1.2 PEG 300

- 5 The steps followed while evaluating the solubility with PEG 300 are presented in Table 2.2.

Table 2.2: Solubility enhancement with PEG 300

Step. No.	Component Added	Weight (g) added	Total cumulative amount (g)	Appearance of the solution
1	API	9.009	9.009	NAP
2	Water	5.268	14.278	Slurry was formed with undissolved TXA
3	PEG 300	2.041	16.319	White solution with undissolved TXA
4	PEG 300	1.998	18.317	White solution with undissolved TXA
5	PEG 300	2.001	20.317	White solution with undissolved TXA
6	PEG 300	1.999	22.316	White solution with undissolved TXA
7	PEG 300	2.990	25.306	White solution with undissolved TXA
8	PEG 300	3.015	28.321	White solution with undissolved TXA
9	PEG 300	3.008	31.329	White solution with undissolved TXA
10	PEG 300	3.009	34.338	White solution with undissolved TXA
11	PEG 300	5.024	39.361	White solution with undissolved TXA
12	PEG 300	5.040	44.401	White solution with undissolved TXA
13	PEG 300	4.988	49.389	White solution with undissolved TXA
14	PEG 300	10.006	59.394	White solution with undissolved TXA
15	PEG 300	19.940	79.334	White solution with undissolved TXA
Final weight of the solution (g)			79.3 g	
Weight of solubilizer (PEG 300) in g			65.1 g	
Weight percent of solubilizer (%w/w)			82.0 % w/w	

A clear solution was not achieved even after taking the PEG 300 content up to 82% of the final weight of the solution, which was 79.3 g. After the last addition, mixing of the solution

continued for approx. 30 minutes. The required volume (10 mL) of the solution was then filtered by using a PVDF syringe filter and tested for Assay.

2.1.3 Propylene Glycol

- 5 The steps followed while evaluating the solubility with propylene glycol are presented in Table 2.3.

Table 2.3: Solubility enhancement with propylene glycol

Step. No.	Component Added	Weight (g) added	Total cumulative amount (g)	Appearance of the solution
1	API	9.004	9.004	NAP
2	Water	4.999	14.003	Slurry was formed with undissolved TXA
3	Propylene Glycol	2.006	16.009	White solution with undissolved TXA
4	Propylene Glycol	2.022	18.031	White solution with undissolved TXA
5	Propylene Glycol	2.016	20.047	White solution with undissolved TXA
6	Propylene Glycol	2.005	22.052	White solution with undissolved TXA
7	Propylene Glycol	3.018	25.070	White solution with undissolved TXA
8	Propylene Glycol	3.012	28.082	White solution with undissolved TXA
9	Propylene Glycol	3.007	31.089	White solution with undissolved TXA
10	Propylene Glycol	2.993	34.082	White solution with undissolved TXA
11	Propylene Glycol	5.019	39.101	White solution with undissolved TXA
12	Propylene Glycol	4.998	44.099	White solution with undissolved TXA
13	Propylene Glycol	5.022	49.121	White solution with undissolved TXA
14	Propylene Glycol	9.998	59.119	White solution with undissolved TXA
15	Propylene Glycol	19.960	79.079	White solution with undissolved TXA
Final weight of the solution (g)			79.1 g	
Weight of solubilizer (propylene glycol) in g			65.1 g	
Weight percent of solubilizer (%w/w)			82.3 % w/w	

- 10 A clear solution was not achieved even after taking the propylene glycol content up to 82.3% of the final weight of the solution, which was 79.1 g. After the last addition, mixing of the

solution continued for approx. 30 minutes. The required volume (10 mL) of the solution was then filtered by using a PVDF syringe filter and tested for Assay.

2.1.4 Captisol

- 5 The steps followed while evaluating the solubility with Captisol are presented in Table 2.4.

Table 2.4: Solubility enhancement with Captisol

Step. No.	Component Added	Weight (g) added	Total cumulative amount (g)	Appearance of the solution
1	API	9.005	9.005	NAP
2	Water	5.062	14.067	Slurry was formed with undissolved TXA
3	Captisol	2.004	16.071	White solution with undissolved TXA
4	Captisol	2.002	18.074	Captisol is not getting mixed into the solution. Hence WFI was added.
5	Water	1.952	20.025	White solution with undissolved TXA
6	Captisol	1.998	22.023	Captisol is not getting mixed into the solution. Hence WFI was added.
7	Water	1.963	23.986	White solution with undissolved TXA
8	Captisol	1.986	25.973	Captisol is not getting mixed into the solution. Hence WFI was added.
9	Water	1.952	27.925	White solution with undissolved TXA
10	Captisol	2.003	29.927	Captisol is not getting mixed into the solution. Hence WFI was added.
11	Water	1.946	31.873	White solution with undissolved TXA
12	Water	1.945	33.818	White solution with undissolved TXA
13	Captisol	1.981	35.799	White solution with undissolved TXA
14	Water	4.957	40.756	White solution with undissolved TXA
15	Water	9.921	50.677	White solution with undissolved TXA
16	Captisol	2.004	52.681	White solution with undissolved TXA
Final weight of the solution (g)			52.7 g	
Weight of solubilizer (Captisol) in g			14.0 g	
Weight percent of solubilizer (%w/w)			26.5 % w/w	

After the last addition, mixing of the solution continued for approx. 30 minutes. The required volume (10 mL) of the solution was then filtered by using a PVDF syringe filter and tested for Assay.

10

2.1.5 Kolliphor EL

The steps followed while evaluating the solubility with Kolliphor EL are presented in Table 2.5.

Table 2.5: Solubility enhancement with Kolliphor EL

Step No.	Component Added	Weight (g) added	Total cumulative amount (g)	Appearance of the solution
1	API	9.002	9.002	NAP
2	Water	5.058	14.061	Slurry was formed with undissolved TXA
3	Kolliphor EL	2.069	16.130	White gel type solution with undissolved TXA
4	Kolliphor EL	2.005	18.134	Sticky gel type of solution was formed. Hence, WFI was added.
5	Water	3.892	22.026	White gel type solution with undissolved TXA
6	Kolliphor EL	1.996	24.022	Sticky gel type of solution was formed. Hence, WFI was added.
7	Water	1.967	25.989	White gel type solution with undissolved TXA
8	Kolliphor EL	2.014	28.003	Sticky gel type of solution was formed. Hence, WFI was added.
9	Water	1.946	29.949	White gel type solution with undissolved TXA
10	Kolliphor EL	2.003	31.952	Sticky gel type of solution was formed. Hence, WFI was added.
11	Water	1.949	33.901	Sticky gel type of solution was formed. Hence, WFI was added.
12	Water	1.967	35.868	Sticky gel type of solution was formed. Hence, WFI was added.
13	Water	5.055	40.924	Sticky gel type of solution was formed.
Final weight of the solution (g)			40.9 g	
Weight of solubilizer (Kolliphor EL) in g			10.1 g	
Weight percent of solubilizer (%w/w)			24.6 % w/w	

- 5 A sticky gel type of solution was formed at the end of mixing and the solution was not filterable. Hence the sample was not tested for assay.

2.2 Solubility enhancer screening

- The solubility of TXA achieved by using different solubility enhancers is presented in Table 2.6. TXA has very low solubility in the presence of solubility enhancers, when compared to its literature quoted solubility in purified water of approx. 167 mg/mL (<https://www.scbt.com/p/tranexamic-acid-1197-18-8>). The TXA concentrations in the formulated solution containing the solubility enhancers were so low that it was not possible to analyse them for related substances.

Table 2.6: Assay data with solubility enhancers

Sample No.	Solubility enhancer	Concentration (mg/mL)
1	Glycerol	23.42
2	PEG 300	0.42
3	Propylene Glycol	4.14
4	Captisol	103.73
5	Kolliphor EL	NA

2.3 Development stability study on solubility enhancement systems

A development stability study was not performed on the solutions prepared with the solubility enhancers as the solubility of TXA was observed to be very low in the presence of solubility enhancers, when compared to the solubility of TXA in water.

2.4 Conclusions

TXA has very low solubility in presence of solubility enhancers compared with its solubility in water (approx. 167 mg/mL). Data generated demonstrated that the evaluated solubilizers (Propylene Glycol, PEG 300, Glycerol, Kolliphor EL and Captisol) were not suitable for enhancing the solubility of TXA.

In conclusion, the data provided in Examples 1 and 2 provides compelling evidence that a formulation at pH 4.0 without solubility enhancers is optimal for the development of a stable, high concentration TXA DP.

EXAMPLE 3

3.1 Determination of Saturation solubility

A 5% w/v solution of Ph Eur/BP grade TXA API in water should have a pH of 7.0 to 8.0. However, the present inventors have found that TXA is very soluble at acidic pH, especially around pH 4.0. Hence, the use of acid solutions for dissolution of TXA and for adjusting the pH to the target value was evaluated. As the target is to achieve high concentrations of TXA in the proposed DP formulations, a higher volume of acid stock solution will be required to overcome the pH contribution by higher concentration of TXA and to maintain the lower pH 4.0.

In general, for lower concentration DPs, the standard approach is to dissolve the API and then adjust the pH. This approach, for higher concentration DPs, will lead to the dilution of the TXA concentration. Hence, to avoid the dilution of the TXA concentration upon addition

of acid stock solution, adding TXA directly to the acid stock solution (as the solvent) was evaluated.

5 A saturation solubility study was performed to assess the maximum solubility of TXA that could be achieved by using different strengths of acid stock solutions i.e., 4N, 5N and 6N HCl solutions.

3.1.1 Determination of Saturation solubility by using 6N HCl solution

10 The initial saturation solubility experiment was performed by using 6N HCl solution to determine the maximum TXA solubility that could be achieved.

The steps followed for the determination of the saturation solubility are presented below:

- 1) 50 mL glass beaker was taken, and a magnetic stir bar (3 cm) was added to the beaker. The weight of beaker + stir bar was recorded for information only.
- 15 2) 10 mL of 6N HCl solution was taken into the 50 mL glass beaker and approximately 1g weighed quantities of TXA were added.
- 3) The first 1g of TXA added dissolved immediately and a clear solution was obtained.
- 4) Additional 1g quantities of TXA were added under continuous stirring. Eventually, an opalescent solution was obtained with undissolved TXA, which remained undissolved even
- 20 after mixing for an additional 15 minutes at 250 rpm.

Note: pH was monitored while adding the API. The pH values were negative (pH value was -0.49, after addition of approx. 3 g of TXA) due to the strength of the acid solution.

- 5) An additional 1g of TXA was added to ensure an excess quantity of API was present while determining the saturation solubility. Mixing was continued for a further 60 minutes after
- 25 which the solution was filtered using a PVDF syringe filter. The filtered solution was tested for assay and related substances (by using HPLC Method A). The results are summarised in Tables 3.1, 3.2 and 3.3.

3.1.2 Determination of Saturation solubility by using 5N HCl solution

30 The saturation solubility was also assessed using 5N HCl solution. The steps followed for the determination of the saturation solubility using 5N HCl are presented below:

- 1) 50 mL glass beaker was taken and a magnetic stir bar (3 cm) was added to the beaker. The weight of beaker + stir bar was recorded for information only.

- 2) 8 mL of 5N HCl solution was taken into the 50 mL glass beaker and to this, 10 g of TXA was added slowly under continuous stirring (300 RPM). pH was monitored after addition of API to ensure that the pH was within the defined range.
- 3) The mixing was continued for 60 minutes at 300 RPM, then the solution was filtered by using a PVDF syringe filter. The filtered solution was tested for pH, density, assay and related substances (by using HPLC Method A). The results are summarised in Tables 3.1, 3.2 and 3.3.

3.1.3 Determination of Saturation solubility by using 4N HCl solution

- The saturation solubility was also assessed using 4N HCl solution The steps followed for the determination of the saturation solubility by using 4N HCl are presented below:
- 1) 50 mL glass beaker was taken, and a magnetic stir bar (3 cm) was added to the beaker. The weight of beaker + stir bar was recorded for information only.
- 2) 10 mL of 4N HCl solution was taken into the 50 mL glass beaker and to this, 10g of TXA was added slowly under continuous stirring (300 RPM). pH was monitored after addition of API to ensure that, the pH was within the defined range.
- 3) The mixing was continued for 60 minutes at 300 RPM, then the solution was filtered by using a PES syringe filter. The filtered solution was tested for pH, assay and related substances (by using HPLC Method B). The results are summarised in Tables 3.1, 3.2 and 3.3.

3.2 Results of the saturation solubility determination

The observations and the in-process data for the saturation solubility determination using 6N, 5N and 4N HCl are presented in Table 3.1

Table 3.1: In-process data of saturation solubility experiment

Description of the Steps	6N HCl	5N HCl	4N HCl
Volume of HCl solution taken (mL)	10 mL	8 mL	10mL
Amount of API added (g)	3.02 g (added approx. 1 g each for 3 times)	10 g (single addition)	10.02g
Appearance after mixing	Opalescent solution with undissolved particles	Opalescent solution with undissolved particles	Solution with undissolved particles

pH	-0.49	3.91	4.16
Final pH	Not measured	3.86	4.01
Final Osmolality (mOSm/Kg)	Not measured	Not measured	Not measured
Final Density	Not measured	1.124 g/mL	Not measured

The saturation solubility data (assay) obtained with different strengths of acid solution is presented in Table 3.2 and the corresponding % total impurity data is presented in Table 3.3.

- 5
- According to the obtained concentration values, it seems that all the API has been solubilised despite the presence of particulate matter indicating that the particles observed are not undissolved API.

Table 3.2: Saturation solubility data (assay)

Serial number	Sample Description	Concentration (mg/mL)*	Theoretical concentration if all the API would be solubilized (mg/mL)
1	Saturation Solubility with 6N HCl	195.9	≈200
2	Saturation Solubility with 5N HCl	577.9	≈590
3	Saturation Solubility with 4N HCl	548.0	≈546

10

*saturation solubility may not have been completely achieved.

Table 3.3: Data of total impurities

Serial number	Sample Description	% Total impurity
1	Saturation Solubility with 6N HCl	1.47
2	Saturation Solubility with 5N HCl	1.14
3	Saturation Solubility with 4N HCl	1.61

15

3.3 Conclusions

The solubility of TXA at pH 4 is > 500 mg/mL. The observed particulate matter is not thought to be API and instead is due to particulate matter in the API preparation.

EXAMPLE 4**4.1 Optimization of formulation process by using 4N HCl solution****4.1.1 DP target concentration 500 mg/mL**

- 5 Initially, the 4N HCl solution was evaluated to assess whether a DP formulation with a TXA concentration of 500 mg/mL could be achieved.

The steps followed for process optimization by using 4N HCl are presented below:

- 1) 50 mL glass beaker was taken and magnetic stir bar (20 mm) was added to the beaker. The weight of beaker + stir bar was recorded.
- 10 2) 10 mL of 4N HCl solution was taken into the 50 mL glass beaker. With a planned batch size of 20 mL, 10.0 g of TXA was added slowly under continuous stirring.
- 3) Mixing was continued for 30 minutes at 300 rpm, after which it was verified visually that the solution still contained undissolved particles. Hence, an additional quantity of 4N HCl solution was added to dissolve the remaining particles. The batch was made to 100% by
15 adding 4N HCl to dissolve the remaining particles. Even after reaching the planned batch size of 20mL, the solution still contained undissolved particles. As the final batch size had been reached, 80 µL of concentrated HCl (37%) was added to see if the residual particles could be solubilised in a more acidic environment.
- 4) After all the particles were dissolved, the solution was filtered by using a PVDF
20 syringe filter. The filtered solution was tested for pH, density and osmolality. The results are summarised in Table 4.1.

4.1.2 DP target concentration 450 mg/mL

- 25 A similar exercise was conducted at a DP target TXA concentration of 450 mg/mL. The steps followed for process optimization by using 4N HCl are presented below:

- 1) 50 mL glass beaker was taken, and magnetic stir bar (2 cm) was added to the beaker. The weight of beaker + stir bar was recorded.
- 2) 10 mL of 4N HCl solution was taken into the 50 mL glass beaker. With a planned batch size of 20 mL, 9.01 g of TXA was added slowly under continuous stirring.
- 30 3) Mixing was continued for 30 minutes at 250 rpm, after which it was verified visually that the solution still contained undissolved TXA. Hence, an additional 0.6 mL of 4N HCl solution was added to dissolve the remaining TXA.

4) After the complete dissolution of the TXA, 35.3 g of WFI was added to the final batch size of 100%. Then, the solution was filtered by using a PVDF syringe filter. The filtered solution was tested for pH, density and osmolality. The results are summarised in Table 4.1.

5 **4.1.3 DP target concentration 400 mg/mL**

To further understand the solubility of TXA in 4N HCl solution, a further exercise was conducted at a DP target TXA concentration of 400 mg/mL.

The steps followed for process optimization by using 4N HCl are presented below:

- 1) 50 mL glass beaker was taken, and magnetic stir bar (2 cm) was added to the beaker.
- 10 The weight of beaker + stir bar was recorded.
- 2) 10 mL of 4N HCl solution was taken into the 50 mL glass beaker. With a planned batch size of 20 mL, 7.99 g of TXA was added slowly under continuous stirring.
- 3) Mixing was continued for 30 minutes at 300 rpm, after which it was verified visually that the TXA had completely dissolved. Then WFI was added to reach the final batch size of
- 15 20 mL.
- 4) After the complete dissolution of the TXA, the solution was filtered by using a PVDF syringe filter. The filtered solution was tested for pH, density and osmolality. The results are summarised in Table 4.1.

20 **4.2 Optimization of formulation process by using 5N HCl solution**

In the previous work, undissolved TXA API was observed in the final batch size targeting a TXA concentration of 500 mg/mL by using 4N HCl solution (refer to section 4.1.1). Concentrated acid was added to achieve full solubilisation. Hence process optimization was performed by using 5N HCl solution with a final target TXA concentration of 500 mg/mL.

25 The steps to be followed for the formulation process optimization by using 5N HCl solution are presented below:

- 1) 50 mL glass beaker was taken, and magnetic stir bar (3 cm) was added to the beaker. The weight of beaker + stir bar was recorded.
- 2) 8 mL (40% of final batch size) of 5N HCl solution was taken into the 50 mL glass
- 30 beaker. With a planned batch size of 20 mL, 10.0 g of TXA was added slowly under continuous stirring.
- 3) Mixing was continued for 30 minutes at 300 rpm, after which it was verified visually that the solution still contained undissolved particles. An opalescent solution was observed

with undissolved particles. Hence, a further 2 mL of 5N HCl solution was added to dissolve the remaining TA.

- 4) After the complete dissolution of the particles, WFI was added to make the 20ml final batch size. The solution was filtered by using a PVDF syringe filter. The filtered solution was tested for pH, density, osmolality, assay and related substances (by using HPLC Method). The results are summarised in Table 4.2.

4.3 Results

The in-process (IPC) data and the observations generated during process optimization by using 4N HCl and 5N HCl solution are presented in Tables 4.1 and 4.2 respectively.

Table 4.1: IPC data and observations of the process optimization work with 4N HCl solution

Description of the Steps	DP target concentration 500 mg/mL	DP target concentration 450 mg/mL	DP target concentration 400 mg/mL
Volume of 4N HCl taken (mL)	10	10	10
Amount of API added (g)	10.0	9.01	7.99
Appearance after mixing	Undissolved particles with pH 4.11 (23.3°C)	Undissolved particles with pH 4.09 (24.3°C)	API Dissolved with visible fiber like materials. The pH is 3.89 (24.5°C).
API Dissolution and 100% batch size	Added 4N HCl to make 100% batch size (20 mL). Undissolved API was present with pH 4.07 (23.5°C). Added 80 µL of 37% HCl under continuous stirring to dissolve the undissolved particles. Particles were completely dissolved (no API crystal were seen but big fiber like materials were present) and the pH was 4.04 (23.6°C).	Added 0.6 mL of 4N HCl and the pH was 4.02 and most of the particle was dissolved. Added WFI to the 100% batch size (20 mL) and the particles were dissolved completely (no API crystal were seen but fiber like materials were present)	WFI added to reach the final size of 20 mL (by volumetric approach). No pH adjustment was performed.
Final pH	4.03 at 23.9°C	3.94 at 23.4°C	3.88 at 24.3°C
Final Osmolality (mOsm/Kg)	4983 (997 mOsm/Kg & dilution factor is 5)	4430 (886 mOsm/Kg & dilution factor is 5)	3670 (734 mOsm/Kg & dilution factor is 5)

Final Density	1.1170 g/mL at 24.8°C	1.1099 g/mL at 24.0°C	1.0902 g/mL at 24.8°C
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Table 4.2: IPC data and observations of the process optimization work with 5N HCl solution (500 mg/mL)

Description of the Steps	DP target concentration 500mg/mL
Volume of 5N HCl taken (mL)	8 mL
Amount of API added (g)	10 g for 20 mL batch size
Appearance after mixing	Opalescent solution with undissolved particles*.
API Dissolution and 100% batch size	Added 2 mL of 5N HCl solution to dissolve the particles and then added WFI to the 100% batch size (20 mL).
Final pH	3.86 at 23.9°C
Final Osmolality (mOSm/Kg)	4608 (1152 mOsm/Kg & dilution factor is 4)
Final Density	1.1162 g/mL at 24.2°C

*It is noted that saturation solubility may not have been completely achieved.

5

Despite the presence of undissolved particles, the solution concentration reaches the target value suggesting that these particles are not API. Furthermore, it should be noted that the presence of undissolved API at 500 mg/mL would not be consistent with the saturation solubility results for 4N HCl.

10

The chromatographic data of assay and related substances (tested by HPLC Method A outlined) of DP with target concentration 500 mg/mL is presented in Tables 4.3 and 4.4 respectively, along with the data for DP with target concentration 450 mg/mL and the data for DP with target concentration 400 mg/mL. This data confirmed no considerable impact of

15

Table 4.3: Data of assay

Serial number	Sample Description	Concentration (mg/mL)
1	DP target concentration 500 mg/mL prepared by using 5N HCl as the solvent	505.4
2	DP target concentration 450 mg/mL prepared by using 4N HCl as the solvent*	448.7
3	DP target concentration 400 mg/mL prepared by using 4N HCl as the solvent*	425.2

Table 4.4: Data of total impurities

Serial number	Sample Description	% Total impurity
1	DP target concentration 500 mg/mL prepared by using 5N HCl as the solvent	1.11
2	DP target concentration 450 mg/mL prepared by using 4N HCl as the solvent*	1.10
3	DP target concentration 400 mg/mL prepared by using 4N HCl as the solvent*	1.08

3.4 Conclusions

By adding TXA to stock acid solutions it was possible to prepare DP having a TXA concentration > 500 mg/mL at a pH of around 4.

5

EXAMPLE 5

5.1 Stability Study

- 10
- Two batches of Tranexamic acid Drug Product were prepared and samples from each batch subjected to a stability study. The aim of the study was to investigate the product behaviour against temperature, humidity and time, and collect preliminary data to assess the DP shelf life.
- 15
- Each DP sample was a liquid formulation of 455 mg/ml Tranexamic acid with a volume equal to 2.45mL (overfill included) and a target pH of 4 ± 0.2. The composition of the liquid 455 mg/ml Tranexamic acid formulation is shown in Table 5.1 below.

Table 5.1: Composition of 455mg/ml TXA DP formulated solution

INGREDIENT	CONCENTRATION
Tranexamic acid	455 mg/ml
4.0 N hydrochloric acid	Solution necessary for adjustment to the target pH of 4.0 at T=23-25°C (acceptable range 3.8-4.2)
1.0 N Sodium hydroxide	Solution necessary for pH adjustment to the target pH of 4.0

	at T=23-25°C (acceptable range 3.8-4.2)
WFI	Q.S to 1.0 mL

5.2 455mg/ml TXA DP Preparation

5 The liquid formulation of 455 mg/ml Tranexamic acid was prepared in accordance with the method of the present invention. The preparation method for Batch 1 and Batch 2 of the 455 mg/ml TXA DP formulation is set out below.

10 Batch 1- Preparation Method

Batch 1 was manufactured with a target batch size of 2.2L. The target amount of TXA per batch was 1001.0 g ± 0.5%.

- 15
- 1) 5L glass beaker was taken, and magnetic stir bar (7 cm) was added to the beaker. The weight of the beaker + the stir bar was recorded.
- 2) 1216.6 g of 4N HCl solution was taken into the 5L glass beaker. With a planned batch size of 2.2 L, 1002.17 g of TXA was added slowly under continuous stirring.
- 3) Mixing was continued for 1 hour 42 minutes at 400 rpm, after which it was verified
- 20 visually that the solution contained dissolved TXA.
- 4) After the dissolution of the TXA, 216.9 g of WFI was added to the final batch size of 100%. Then, the solution was filtered by using a PES 0.22 µm filter.

Batch 2 - Preparation Method

25

Batch 2 was manufactured with a target batch size of 7.5L. The target amount of TXA per batch was 3412.5 g ± 0.5%.

- 30
- 1) 10L glass beaker was taken, and magnetic stir bar (7.5 cm) was added to the beaker. The weight of the beaker + the stir bar was recorded.

- 2) 4147.6 g of 4N HCl solution was taken into the 10L glass beaker. With a planned batch size of 7.5 L, 3413.7 g of TXA was added slowly under continuous stirring.
 - 3) Mixing was continued for 3hours at 500 rpm, after which it was verified visually that the solution contained dissolved TXA.
 - 5 4) After the dissolution of the TXA, the solution was filtered by using a PVDF 0.45 µm filter
 - 5) 818.81 g of WFI was added to the final batch size of 100%. Then, the solution was filtered by using a PES 0.22 µm filter.
- 10 During the preparation of Batch 1 it was observed that the solution obtained after step 3 (after the TXA had been added, mixed and dissolved) had an opalescence appearance. In order to optimise the process, in particular to facilitate downstream analysis, it was decided to add an additional filtration step in the preparation of Batch 2. The additional filtration step was added after the TXA had dissolved in solution and before adding WFI to bring the batch up
- 15 to size. It was found that this additional filtration step removed the opalescence appearance to produce a clear solution at this stage.

The stability results in section 5.4 below indicate that the opalescence appearance observed in step 3 of Batch 1 method does not impact the final appearance of the formulation (colourless) nor its stability. Therefore, the preparation methods of Batch 1 and Batch 2 are

20 both suitable routes to obtain stable 455 mg/ml TXA formulations at pH 4.

5.3 Storage Conditions

- 25 Samples from Batch 1 and Batch 2 of the TXA DP were stored under the following conditions in an upright orientation:
- 25 °C /60 % RH: long-term storage condition
 - 30 °C/ 75 % RH: intermediate storage condition
 - 30 • 40 °C/ 75 % RH: accelerated storage condition

5.4 Results

The total duration of the stability study is 24 months. Data up to T=12M for batch 1 and T=9M for batch 2 is currently available.

5

5.4.1 Appearance and pH

The general appearance of the DP samples (visible particles, color, and clarity) and their pH were measured at different time points under long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions. The data collected for batch 1 DP samples is shown in Tables 5.2-5.4 and the data collected for batch 2 DP samples is shown in Tables 5.5-5.7. Table 5.8 summarises the acceptance criteria for the appearance and pH parameters.

15 Table 5.2: Batch 1 - Results for stability samples stored at 25 ± 2 °C / 60 ± 5% RH

Analytical Parameter	T=0	T=2M	T=3M	T=6M	T=9M	T=12M
Appearance of solution (visible particles, color, and clarity)	A clear, and colourless liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates
pH	3.8	4.0	4.0	3.9	3.8	3.9

Table 5.3: Batch 1 - Results for stability samples stored at 30 ± 2 °C / 75 ± 5% RH

Analytical Parameter	T=0	T=1M	T=2M	T=3M	T=6M	T=9M	T=12M
Appearance of solution (visible particles, color, and clarity)	A clear and colourless liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates
pH	3.8	4.0	4.0	4.0	3.8	3.8	3.8

Table 5.4: Batch 1 - Results for stability samples stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH

Analytical Parameter	T=0	T=1M	T=2M	T=3M	T=6M	T=9M	T=12M
Appearance of solution (visible particles, color, and clarity)	A clear and colourless liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates
pH	3.8	4.0	4.0	4.0	3.8	3.9	3.9

Table 5.5: Batch 2 - Results for stability samples stored at $25 \pm 2^\circ\text{C}$ / $60 \pm 5\%$ RH

Analytical Parameter	T=0	T=1M	T=2M	T=3M	T=6M	T=9M
Appearance of solution (visible particles, color, and clarity)	A clear and colourless liquid with no visible particulates	A clear and colourless liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates
pH	4.0	3.9	4.0	3.8	3.9	3.9

5 Table 5.6: Batch 2 - Results for stability samples stored at $30 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH

Analytical Parameter	T=0	T=1M	T=2M	T=3M	T=6M	T=9M
Appearance of solution (visible particles, color, and clarity)	A clear and colourless liquid with no visible particulates	A clear and colourless liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates	A clear and pale yellow liquid with no visible particulates
pH	4.0	3.9	3.8	3.8	3.9	3.8

Table 5.7: Batch 2 - Results for stability samples stored at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH

Analytical Parameter	T=0	T=1M	T=2M	T=3M	T=6M	T=9M
Appearance of solution	A clear and colourless liquid with	A clear and pale yellow liquid with	A clear and pale yellow liquid with	A clear and pale yellow liquid with	A clear and pale yellow liquid with	A clear and pale yellow liquid with

(visible particles, color, and clarity)	no visible particulates	no visible particulates	no visible particulates	no visible particulates	no visible particulates	no visible particulates
pH	4.0	3.9	3.8	3.8	3.9	3.8

Table 5.8: Acceptance criteria – Appearance and pH

Analytical Parameter	Acceptance Criteria
Appearance of solution (visible particles, color, and clarity)	A clear, colourless to pale yellow liquid with no visible particulates
pH	4.0 ± 0.2

- 5
- Appearance of the solution complies with acceptance criteria throughout the duration of the stability test for batch 1 and batch 2 samples at long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions. Appearance of the solution was measured against white and black backgrounds (no specific method available).
- 10
- pH remains within ± 0.2 units of the target pH value 4 throughout the duration of the stability test for batch 1 and batch 2 samples at under long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions.

5.4.2 Osmolality

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The osmolality of DP samples (Batch 1 and 2) was measured for information purposes only at T=0. For DP Batch 1 an osmolality of Dil. 1/4 – 1197 Osm/Kg and Dil. 1/6 – 858 Osm/Kg was observed. For DP Batch 2 an osmolality of Dil. 1/4 – 1166 Osm/Kg and Dil. 1/6 – 745 Osm/Kg was observed.

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5.4.3 Assay for concentration of DP

- 25
- The assay for concentration of DP samples (Batch 1 and 2) was monitored throughout the duration of the stability test at long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions. Table 5.9 shows the assay values at

T=9M and T=12M for Batch 1 DP samples and Table 5.10 shows the assay values at T= 9M for Batch 2 DP samples. The assay values are shown as a % of the initial DP concentration of 455 mg/ml. As can be observed, the assay values recorded across the different batches and storage conditions remained within the acceptance criteria of 90.0% -110.0%.

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Table 5.9: Batch 1 – Assay data at T=9M and T=12M

Storage conditions	Assay at T=9M	Assay at T=12M
25 ± 2 °C / 60 ± 5% RH	99.2 %	105.0%
30 ± 2 °C / 75 ± 5% RH	100.7%	104.8%
40 ± 2 °C / 75 ± 5% RH	98.4%	106.5%

Table 5.10: Batch 2 – Assay data at T=9M

Storage conditions	Assay at T=9M
25 ± 2 °C / 60 ± 5% RH	106.3%
30 ± 2 °C / 75 ± 5% RH	104.2%
40 ± 2 °C / 75 ± 5% RH	107.1%

10

5.4.4 Related substances

Related substances were measured (by HPLC) throughout the duration of the stability test at long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions and were found to meet the following acceptance criteria:

- Impurity A: NMT 1%
- Impurity B: NMT 0.5%
- Impurity C: NMT 0.1%

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- Impurity D: NMT 0.1%
- Secondary peaks: NMT 0.1%

5.5 Conclusions

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The stability data provides evidence that DP formulation 455mg/mL TXA at pH 4 is stable under long-term (25 °C /60 % RH), intermediate (30 °C/ 75 % RH) and accelerated (40 °C/ 75 % RH) storage conditions. In particular, the DP formulation 455mg/mL TXA of the present invention has a stable pH of 4 ± 0.2 up to at least T=9M. The appearance, assay and related substances of the DP formulation 455mg/mL TXA are also within the stability acceptance criteria up to at least T=9M. Batch 1 results show that DP samples can maintain stability up to T=12M.

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EXAMPLE 6

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US 2023/0248643A1 provides formulations of tranexamic acid at a concentration of 500 mg/ml and a pH of 3-4 (Formulations A-C). Formulation A is a 500mg/ml TXA, 0.9% aq. sodium chloride composition. Formulation B is a 500mg/ml TXA, 4% aq. benzyl alcohol composition and Formulation C is a 500mg/ml TXA aqueous composition.

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In US 2023/0248643A1 pH stability data at room temperature and accelerated conditions up to T=6 months is provided for Formulation A in Table 4 (formulation comprising NaCl). It can be observed from the data provided that the pH after 6 months of storage has decreased at least by 0.32 from the starting pH of 4.02. This change in pH is much greater than the ± 0.2 stability acceptance criteria achieved by the claimed compositions. No stability data is provided for Formulations B and C.

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6.1 Comparative Study

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The most structurally similar formulation described in US 2023/0248643A1 to the formulation of the present invention is Formulation C (a 500mg/ml TXA aqueous composition without excipients, see paragraphs [00186]-[00188]). A comparative study to assess the stability of Formulation C of US 2023/0248643A1 and the 455mg/ml TXA DP formulation of the present

invention (Formulation D) at ambient temperature (18-25°C) and refrigeration temperature (2-8 °C) was conducted.

6.1.2 Formulation Preparation

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Formulation C and D were prepared at ambient temperature (18-25°C) by dissolving TXA in an acidic vehicle and stored overnight at a temperature of 2-8 °C. The target compositions of each formulation are shown in Tables 6.1 and 6.2 below:

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Table 6.1 - Composition of each formulation by concentration

Component	Formulation C	Formulation D (formulation of the invention)
	Concentration	
Tranexamic Acid (TXA)	500 mg/ml	455 mg/ml
37% HCl to target pH	<i>q.s.</i>	<i>q.s.</i>
NaOH (1N) to target pH	<i>q.s.</i>	<i>q.s.</i>
Water for injection (WFI)	<i>q.s. to volume</i>	<i>q.s. to volume</i>
Target pH	3.5 ± 0.5	4.0 ± 0.2

Table 6.1 - Composition of each formulation by mass

Component	Formulation C	Formulation D (formulation of the invention)
	Concentration	
Tranexamic Acid (TXA)	100	91
37% HCl to target pH	<i>q.s.</i>	<i>q.s.</i>
NaOH (1N) to target pH	<i>q.s.</i>	<i>q.s.</i>
Water for injection (WFI)	<i>q.s. to volume</i>	<i>q.s. to volume</i>
Target pH	3.5 ± 0.5	4.0 ± 0.2
Total	200	200

6.2 Observations

6.2.1 Formulation C – DP target concentration 500 mg/ml (pH 3.5)

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At ambient temperature, a clear formulation with all TXA in solution was obtained. However, upon overnight storage at 2-8°C, precipitation was observed (see crystalline material in Figure 1B). The crystalline material observed did not completely re-dissolve when equilibrated at ambient temperature. This demonstrates some instability of Formulation C at low temperatures and that once exposed to low temperatures, Formulation C cannot be recovered. The limited stability window of this formulation is a drawback when considering its suitability for intramuscular administration and the treatment of haemorrhage in trauma patients. Use of this formulation may require strict storage and administration conditions.

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6.2.2 Inventive Formulation D – DP target concentration 455 mg/ml (pH 4)

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TXA was fully dissolved at ambient temperature to form a clear solution (see Figure 2A) and the TXA remained in solution even after overnight storage at 2-8 °C (see Figure 2B where no precipitation is observed). Based on the comparison with Formulation C, it appears that for this vehicle a concentration of around 455 mg/ml TXA at pH 4 achieves an advantageous balance between a concentrated TXA formulation suitable for intramuscular administration (in a suitable volume) and stability of the formulation.

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6.3 Conclusions

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Formulation C was achieved with TXA in solution at ambient temperature, however, overnight storage at low temperatures resulted in irreversible precipitation of the solution. This suggests that Formulation C may be relatively unstable at low temperatures. This limited stability may restrict the use and applications of this Formulation.

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Formulation D produced a clear formulation with all TXA in solution. TXA remained in solution at low temperature storage. This evidences that this formulation is convenient to formulate and stable in a range of storage conditions (see also stability data of Example 5).

These observations suggest that TXA in Formulation D is close to the edge of solubility. A higher concentration of TXA, as in Formulation C may result in TXA precipitating out of solution when the temperature is lowered. Therefore, Formulation D achieves an advantageous balance between high TXA concentration and stability.

The present invention will now be described in relation to the following non-limiting clauses:

1. An aqueous pharmaceutical composition comprising tranexamic acid (TXA) or a pharmaceutically acceptable salt thereof, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is greater than about 0.637 M, wherein the pH of the composition is about 3 to about 5.
2. The composition of clause 1, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is greater than 1.06 M, at least about 1.27 M, at least about 1.59 M, at least about 1.91 M, at least about 2.23 M, at least about 2.54 M or at least about 2.86 M.
3. The composition of clause 1 or 2, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is no more than about 3.18 M, no more than about 3.50 M, no more than about 3.68 M or no more than about 3.82 M.
4. The composition of clause 1, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is within about a 25% range around 2.9 M or about 2.54 M to about 3.18 M.
5. The composition of clause 1, wherein the composition comprises TXA at a concentration within about a 25% range around 455 mg/mL.
6. The composition of any one of clauses 1 to 5, wherein the pH of the composition is about 3.5 to about 4.5 or about 3.75 to about 4.25, preferably about 4.
7. The composition of any one of clauses 1 to 6, wherein the composition comprises a pH modifying agent, optionally wherein the pH modifying agent is an acid.
8. The composition of any one of clauses 1 to 7, wherein the composition is substantially free from a pharmaceutical excipient, optionally wherein the pharmaceutical excipient is a solubilizing agent.

9. The composition of any one of clauses 1 to 8 for parenteral administration, preferably for intramuscular administration.
10. The composition of any one of clauses 1 to 9 for use in the treatment or prevention
5 of a disease or disorder in a subject.
11. The composition of any one of clauses 1 to 9 for use in treating or preventing haemorrhage in a subject.
- 10 12. The composition for use of clause 10 or 11, wherein the composition is administered parenterally to the subject, optionally intramuscularly to the subject.
13. The composition for use of any one of clauses 10 to 12, wherein the amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject is within about a
15 10% range around 6.36 mmol.
14. The composition for use of any one of clauses 10 to 13, wherein the composition comprises TXA and the amount of TXA administered to the subject is within about a 10%
20 range around 1g.
15. The composition for use of any one of clauses 10 to 14, wherein the composition is administered to the subject in a single dose.
16. The composition for use of any one of clauses 10 to 15, wherein the volume of the
25 composition administered to the subject is no more than about 5 mL in total, no more than about 4 mL in total, no more than about 3 mL in total, about 1.5 mL to about 2.5 mL in total, about 2 mL to about 2.5 mL in total, preferably about 2.2 mL in total.
17. The composition for use of any one of clauses 10 to 16, wherein the subject has not
30 been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24 hours, 12 hours, 6 hours, 3 hours, 1.5 hours, 1 hour or 0.5 hours.
18. A container containing one dose or a plurality of doses of the composition of any one of clauses 1 to 9 or the composition for use of any one of clauses 10 to 17.

19. The container of clause 18, wherein the amount of TXA or a pharmaceutically acceptable salt thereof in a dose is within about a 10% range around 6.36 mmol.
20. The container of clause 18, wherein the composition comprises TXA and the amount
5 of TXA in a dose is within about a 10% range around 1g.
21. An injection device for single or multiple use, wherein the injection device comprises an injection needle and a container according to any one of clauses 18 to 20.
- 10 22. The injection device of clause 21 for parenteral administration of the pharmaceutical composition, preferably for intramuscular administration.
23. A method of preparing a composition according to any one of clauses 1 to 9, wherein the method comprises:
- 15 (a) providing an aqueous acid solution; and
(b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid solution, optionally wherein the method further comprises adding concentrated acid, further aqueous acid solution, base and/or water until the pH of the solution reaches about 3 to about 5, preferably about 4.
- 20 24. The composition of clause 7 or method of clause 23, wherein the acid is an inorganic acid or organic acid, preferably an inorganic acid such as hydrochloric acid.
25. A method of preparing the container of any one of clauses 18 to 20, wherein the
25 method comprises:
- A) (a) sterilising an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof; and
(b) adding the sterilised solution comprising TXA or a pharmaceutically acceptable salt thereof to a (sterilised) container; or
- 30 B) (a) adding an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof to a container; and
(b) sterilising the container with the aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof comprised therein.

While the invention herein disclosed has been described by means of specific embodiments and applications thereof, numerous modifications and variations could be made thereto by those skilled in the art without departing from the spirit and scope of the present invention.

- 5 Such modifications are understood to be within the scope of the appended claims. Moreover, all embodiments described herein are considered to be broadly applicable and combinable with any and all other consistent embodiments, as appropriate.

- 10 Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

CLAIMS

1. An aqueous pharmaceutical composition comprising tranexamic acid (TXA) or a pharmaceutically acceptable salt thereof and a pH modifying agent, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is within about a 5% range around 2.9 M, or about 2.54 M to about 3.18 M, wherein the pH of the composition is about 4.
2. The composition of claim 1, wherein the concentration of TXA or pharmaceutically acceptable salt thereof in the composition is around 2.9 M.
3. The composition of any one of claims 1 to 2, wherein the pH modifying agent is an acid.
4. The composition of any one of claims 1 to 3, wherein the composition is substantially free from any other pharmaceutical excipient.
5. The composition of any one of claims 1 to 4 for parenteral administration, preferably for intramuscular administration.
6. The composition of any one of claims 1 to 5 for use in the treatment or prevention of a disease or disorder in a subject.
7. The composition of any one of claims 1 to 5 for use in treating or preventing haemorrhage in a subject.
8. The composition for use of claim 6 or 7, wherein the composition is administered parenterally to the subject, optionally intramuscularly to the subject.
9. The composition for use of any one of claims 6 to 8, wherein the amount of TXA or a pharmaceutically acceptable salt thereof administered to the subject is within about a 10% range around 6.36 mmol.

10. The composition for use of any one of claims 6 to 9, wherein the composition comprises TXA and the amount of TXA administered to the subject is within about a 10% range around 1g.
- 5 11. The composition for use of any one of claims 6 to 10, wherein the composition is administered to the subject in a single dose.
12. The composition for use of any one of claims 6 to 11, wherein the volume of the composition administered to the subject is about 1.5 mL to about 2.5 mL in total, about 2 mL
10 to about 2.5 mL in total, preferably about 2.2 mL in total.
13. The composition for use of any one of claims 6 to 12, wherein the subject has not been administered TXA or a pharmaceutically acceptable salt thereof in the previous 24 hours, 12 hours, 6 hours, 3 hours, 1.5 hours, 1 hour or 0.5 hours.
15
14. A container containing one dose or a plurality of doses of the composition of any one of claims 1 to 9 or the composition for use of any one of claims 6 to 13.
15. The container of claim 14, wherein the amount of TXA or a pharmaceutically acceptable salt thereof in a dose is within about a 10% range around 6.36 mmol.
20
16. The container of claim 14, wherein the composition comprises TXA and the amount of TXA in a dose is within about a 10% range around 1g.
17. An injection device for single or multiple use, wherein the injection device comprises
25 an injection needle and a container according to any one of claims 14 to 16.
18. The injection device of claim 17 for parenteral administration of the pharmaceutical composition, preferably for intramuscular administration.
- 30 19. A method of preparing a composition according to any one of claims 1 to 5, wherein the method comprises:
(a) providing an aqueous acid solution; and

(b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid solution,

optionally wherein the method further comprises adding concentrated acid, further aqueous acid solution, base and/or water until the pH of the solution reaches about 4.

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20. The composition of claim 3 or method of claim 19, wherein the acid is an inorganic acid or organic acid, preferably an inorganic acid such as hydrochloric acid.

10 21. A method of preparing the container of any one of claims 14 to 16, wherein the method comprises:

A) (a) sterilising an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof; and

(b) adding the sterilised solution comprising TXA or a pharmaceutically acceptable salt thereof to a (sterilised) container; or

15 B) (a) adding an aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof to a container; and

(b) sterilising the container with the aqueous solution comprising TXA or a pharmaceutically acceptable salt thereof comprised therein.

20 22. A method of preparing a composition according to any one of claims 1 to 5, wherein the method comprises:

(a) providing an aqueous acid solution;

25 (b) adding TXA or a pharmaceutically acceptable salt thereof to the aqueous acid solution to dissolve the TXA and obtain a solution of pH about 4, wherein the acid to TXA ratio is 1.1:1 to 1.3:1 by mass; and

(c) adding water as needed to make up the solution to the final volume.

23. The method of claim 22 wherein the acid is HCl, preferably 4N HCl.

30 24. The method of claim 22 or 23 wherein the acid to TXA ratio is around 1.2:1 by mass.

25. The method of any one of claims 22-24 further comprising filtering the composition.