

HA-based fillers that exhibit desirable stability properties *in vivo*, can be so highly viscous that injection through fine gauge needles is difficult. Conversely, HA-based fillers that are relatively easily injected through fine gauge needles often have relatively inferior stability properties *in vivo*.

[0011] One method to overcome this problem is to use crosslinked HA-based fillers. Crosslinked HA is formed by reacting free HA with a crosslinking agent under suitable reaction conditions. Methods of preparing HA based soft tissue fillers including both crosslinked and free HA are well known.

[0012] It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions. Unfortunately, HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.

[0013] It is an objective of the HA-based soft filler compositions and methods of making and using them as described herein to provide soft tissue fillers that do not cause allergic reactions in patients, are biocompatible and are stable and usable *in vivo* and include one or more local anesthetic agents.

SUMMARY

[0014] The present description relates to soft tissue fillers, for example, dermal and subdermal fillers, based on hyaluronic acid (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). HA-based compositions described herein include a therapeutically effective amount of at least one anesthetic agent. In one example, for example, the anesthetic agent is lidocaine. The present HA-based compositions including at least one anesthetic agent have an enhanced stability, relative to conventional HA-based compositions including, for

example, lidocaine, when subjected to sterilization techniques such as autoclaving, and/or when stored for long periods at ambient temperature. Methods for preparing such HA-based compositions are also provided as well as products made by such methods.

[0014a] In one aspect, the present disclosure refers to a dermal filler comprising: hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and lidocaine; wherein the lidocaine is freely released in vivo; wherein the dermal filler is sterile; and wherein the dermal filler is made by a process comprising: crosslinking HA with BDDE to obtain a crosslinked HA composition; adding lidocaine to the crosslinked HA composition; and heat sterilizing the crosslinked HA composition with added lidocaine to obtain a sterile dermal filler.

[0014b] In another aspect, the present disclosure refers to a dermal filler composition comprising: a composition comprising hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), wherein the HA is not crosslinked to a non-HA biopolymer, and lidocaine; wherein the dermal filler is made by a process comprising: crosslinking HA with BDDE to obtain a crosslinked HA; adding lidocaine to the crosslinked HA; and heat sterilizing the crosslinked HA with added lidocaine to obtain a sterile dermal filler.

[0014c] In another aspect, the present disclosure refers to a dermal filler composition comprising: a hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and about 0.3% lidocaine by weight, wherein the lidocaine is freely released in vivo and wherein the composition is sterile; wherein the composition is made by a process comprising: crosslinking HA with BDDE to obtain a crosslinked HA; adding a free HA gel to the crosslinked HA; adding a solution of lidocaine HCl to the crosslinked HA; and autoclaving the crosslinked HA having free HA gel and lidocaine HCl added thereto, to obtain a sterile dermal filler composition.

[0014d] In another aspect, the present disclosure refers to a dermal filler product comprising: a dermal filler composition comprising a hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and between about 0.1% to about 5.0% lidocaine by weight, wherein the HA is not crosslinked to a non-HA biopolymer, and wherein the composition is sterile; a syringe containing the sterile composition; wherein the product is made by a process comprising: crosslinking HA with BDDE to

obtain a crosslinked HA; adding lidocaine to the crosslinked HA to obtain a crosslinked HA containing lidocaine; and packaging the crosslinked HA containing lidocaine in a syringe; and autoclaving the syringe containing the crosslinked HA containing lidocaine to obtain a dermal filler product.

[0015] Described herein are soft tissue filler compositions, the compositions generally comprising: a hyaluronic acid component crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidylloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, and 1,4-butanediol diglycidyl ether; and at least one anesthetic agent combined with the crosslinked HA component.

[0016] In yet another example, the at least one anesthetic agent is lidocaine. In a further example, the amount of the anesthetic agent is present at a concentration between about 0.1% and about 5.0% by weight of the composition. In still another example, the anesthetic agent is present at a concentration between about 0.2% and about 1.0% by weight of the composition. In one example, the anesthetic agent is lidocaine and is present at a concentration of about 0.3% by weight of the composition.

[0017] In still another example, the soft tissue filler composition has an extrusion force of between about 10 N and about 13 N, for example, at a rate of about 12.5 mm/minute. In yet another example, the composition has a viscosity of between about 5 Pa*s and about 450 Pa*s, for example, when measured at about 5 Hz.

[0018] In one example, the HA component is a gel, for example, a cohesive, hydrated gel. In one example, the HA component is a crosslinked HA gel having no greater than about 1% to about 10% free HA. For purposes of this disclosure, free HA includes truly free HA as well as lightly crosslinked HA chains and fragments, all in soluble form in water.

[0019] In yet other examples, the HA component comprises greater than about 10%, for example, greater than about 15%, for example, up to or greater than about 20% free HA.

[0020] In yet another example, the HA component is a gel comprising particles of crosslinked HA in a relatively fluidic medium of free HA. In some examples, the HA component has an average particle size of greater than about 200 μm , for example, greater than about 250 μm .

[0021] Further described herein is a soft tissue filler composition comprising: a HA component crosslinked with 1,4-butanediol diglycidyl ether (BDDE), said HA component having a degree of crosslinking of less than about 5%, for example, about 2%, and an anesthetic component having a concentration between about 0.1% and about 5.0% by weight of the soft tissue filler composition, wherein the anesthetic is lidocaine.

[0022] Further described herein are methods of preparing soft tissue filler compositions, the methods comprising the steps of: providing a HA component crosslinked with at least one crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyl ether, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane, and 1,4-butanediol diglycidyl ether or combinations thereof; adjusting the pH of said HA component to an adjusted pH above about 7.2; and adding a solution containing at least one anesthetic agent to the HA component having the adjusted pH to obtain a HA-based filler composition.

[0023] In another example, the composition is sterilized, for example, by autoclaving, to form a sterilized composition and wherein the sterilized composition is stable at ambient temperature for at least about months, for example, at least 9 months, at least about 12 months, for example, at least about 36 months, or more.

[0024] In still another example, the adjusted pH is above about 7.5. In another example, the method further comprises the step of homogenizing

the HA component during or after the step of adding the solution containing the at least one anesthetic agent. In a further example, the step of homogenizing comprises subjecting the composition to mixing with a controlled shear.

[0025] In another example, the step of providing a HA component comprises providing dry free NaHA material and hydrating the dry free NaHA material in an alkaline solution to obtain an alkaline, free NaHA gel. In yet another example, the alkaline, free NaHA gel has a pH greater than about 8.0. In still another example the pH is greater than about 10.

[0026] In a further example, the HA component comprises greater than about 20% free HA and the crosslinked portion of the HA component has a degree of crosslinking of less than about 6% or less than about 5%.

[0027] In still a further example, the soft tissue filler composition has a particulate nature in that it comprises particles of crosslinked HA dispersed in a fluid soluble HA medium. In some examples, the average size of such particles is at least about 200 μm , and in other examples the average size of such particles is at least about 250 μm .

[0028] Further described herein is a soft tissue filler composition comprising: a hyaluronic acid (HA) component crosslinked with 1,4-butanediol diglycidyl ether (BDDE), said HA component having a degree of crosslinking of less than about 5%, and an anesthetic component having a concentration between about 0.1% and about 5.0% by weight of the soft tissue filler composition, wherein the anesthetic is lidocaine.

[0029] In a specific example of the disclosure, a method of preparing a soft tissue filler composition is further described, the method comprising the steps of: providing dry free NaHA material and hydrating the dry free NaHA material in an alkaline solution to obtain an alkaline, free NaHA gel; crosslinking the free NaHA gel with BDDE to form a crosslinked alkaline HA composition with a degree of crosslinking less than about 5% and a pH above about 7.2; adding a solution containing lidocaine HCl to the HA component

CLAIMS

1. A dermal filler comprising:
hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and
lidocaine;
wherein the lidocaine is freely released in vivo;
wherein the dermal filler is sterile; and
wherein the dermal filler is made by a process comprising:
 crosslinking HA with BDDE to obtain a crosslinked HA composition;
 adding lidocaine to the crosslinked HA composition; and
 heat sterilizing the crosslinked HA composition with added lidocaine to obtain
a sterile dermal filler.
2. The dermal filler of claim 1, wherein the process further comprises adjusting
the pH of the crosslinked HA composition to obtain an alkaline crosslinked HA
composition.
3. The dermal filler of claim 2, wherein the pH adjustment is performed before
adding the lidocaine.
4. The dermal filler of claim 2, wherein the pH adjustment comprises adjusting
the pH to about 7.5 to about 8.0.
5. The dermal filler of claim 2, wherein the pH adjustment comprises adjusting
the pH to above about 7.5.
6. The dermal filler of claim 1, wherein the adding the lidocaine comprises
adding a solution containing lidocaine HCl.
7. The dermal filler of claim 1, wherein the process further comprises passing the
crosslinked HA composition through a sieve before adding the lidocaine.
8. The dermal filler of claim 7, wherein the process further comprises adding free
HA gel to the crosslinked HA composition after the crosslinked HA composition
has been passed through the sieve.
9. The dermal filler of claim 7, wherein the crosslinked HA composition, after
being passed through the sieve, comprises particles of crosslinked HA having an
average particle size of at least about 200 μm .
10. The dermal filler of claim 7, wherein the crosslinked HA composition, after
being passed through the sieve, comprises particles of crosslinked HA having an
average particle size of at least about 250 μm .

11. The dermal filler of claim 7, wherein the crosslinked HA composition, after being passed through the sieve, comprises particles of crosslinked HA having an average particle size of less than about 200 μm .
12. The dermal filler of claim 1, wherein the process further comprises homogenizing the crosslinked HA composition before adding the lidocaine.
13. The dermal filler of claim 1, wherein the dermal filler has a lidocaine concentration of between about 0.1% and about 5.0% w/w.
14. The dermal filler of claim 1, wherein the dermal filler has a HA concentration between about 20 mg/mL and about 30 mg/mL.
15. The dermal filler of claim 1, having a lidocaine concentration of 0.3% w/w and a HA concentration between about 20 mg/mL and about 30 mg/mL.
16. A dermal filler composition comprising:
a composition comprising hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), wherein the HA is not crosslinked to a non-HA biopolymer, and lidocaine;
wherein the dermal filler is made by a process comprising:
 crosslinking HA with BDDE to obtain a crosslinked HA;
 adding lidocaine to the crosslinked HA; and
 heat sterilizing the crosslinked HA with added lidocaine to obtain a sterile dermal filler.
17. The dermal filler of claim 16, wherein the process further comprises adjusting the pH of the crosslinked HA to obtain an alkaline crosslinked HA.
18. The dermal filler of claim 17, wherein the adjusting the pH is performed before adding the lidocaine.
19. The dermal filler of claim 16, wherein adding the lidocaine comprises adding a solution containing lidocaine HCl.
20. The dermal filler of claim 16, wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of at least about 200 μm .
21. The dermal filler of claim 16, wherein the crosslinked HA comprises particles of crosslinked HA having an average particle size of less than about 200 μm .
22. The dermal filler of claim 16, wherein the dermal filler has a lidocaine concentration of between about 0.1% and about 5.0% w/w.

23. The dermal filler of claim 16, wherein the dermal filler has a HA concentration of between about 20 mg/mL and about 30 mg/mL.
24. A dermal filler composition comprising:
a hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and about 0.3% lidocaine by weight, wherein the lidocaine is freely released in vivo and wherein the composition is sterile;
wherein the composition is made by a process comprising:
 crosslinking HA with BDDE to obtain a crosslinked HA;
 adding a free HA gel to the crosslinked HA;
 adding a solution of lidocaine HCl to the crosslinked HA; and
 autoclaving the crosslinked HA having free HA gel and lidocaine HCl added thereto, to obtain a sterile dermal filler composition.
25. A dermal filler product comprising:
a dermal filler composition comprising a hyaluronic acid (HA) crosslinked with 1,4 butanediol diglycidyl ether (BDDE), and between about 0.1% to about 5.0% lidocaine by weight, wherein the HA is not crosslinked to a non-HA biopolymer, and wherein the composition is sterile;
a syringe containing the sterile composition;
wherein the product is made by a process comprising:
 crosslinking HA with BDDE to obtain a crosslinked HA;
 adding lidocaine to the crosslinked HA to obtain a crosslinked HA containing lidocaine; and
 packaging the crosslinked HA containing lidocaine in a syringe; and
 autoclaving the syringe containing the crosslinked HA containing lidocaine to obtain a dermal filler product.
26. The dermal filler product of claim 25, wherein the sterile composition contained in the syringe has a volume between about 0.8 mL and about 2.5 mL.
27. The dermal filler product of claim 25, wherein the sterile composition has a HA concentration of about 20 mg/mL to about 30 mg/mL.
28. The dermal filler product of claim 25, wherein the sterile composition is stable at ambient temperature for at least about 6 months.
29. The dermal filler product of claim 25, wherein the sterile composition comprises particles of crosslinked HA having an average particle size of at least about 200 μm .
30. The dermal filler product of claim 25, wherein the sterile composition comprises particles of crosslinked HA having an average particle size of less than about 200 μm .