

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 a first aspect, there is provided a method of preparing a soft tissue filler composition, the method comprising the steps of:

providing a hyaluronic acid (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-bisglycidylloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane or combinations thereof, wherein the HA component further comprises uncrosslinked hyaluronic acid (HA) at a concentration of at least 10% of the weight of the hyaluronic acid (HA) component;

adjusting the pH of said hyaluronic acid (HA) component to an adjusted pH above 7.2; and

adding a solution containing at least one anesthetic agent to said hyaluronic acid (HA) component having said adjusted pH to obtain a hyaluronic acid (HA)-based soft tissue filler composition.

[0014b] In a second aspect, there is provided a method of preparing a soft tissue filler composition, the method comprising the steps of:

providing dry uncrosslinked sodium hyaluronate (NaHA) material and hydrating said dry uncrosslinked sodium hyaluronate (NaHA) material in an alkaline solution to obtain an alkaline, uncrosslinked sodium hyaluronate (NaHA) gel;

crosslinking said uncrosslinked sodium hyaluronate (NaHA) gel with BDDE to form a crosslinked alkaline hyaluronic acid (HA) composition with a degree of crosslinking less than 5% and a pH above 7.2;

the crosslinked hyaluronic acid (HA) composition containing greater than 10% uncrosslinked hyaluronic acid (HA) by weight of the composition;

adding a solution containing lidocaine HCl to said hyaluronic acid (HA) component having said adjusted pH to obtain said hyaluronic acid (HA)-based filler composition;

homogenizing said hyaluronic acid (HA)-based filler composition thereby forming a homogenized hyaluronic acid (HA)-based filler composition; and

sterilizing said homogenized hyaluronic acid (HA)-based filler composition thereby forming a sterilized hyaluronic acid (HA)-based filler composition.

[0015] Described herein are soft tissue filler compositions, said compositions generally comprise: a hyaluronic acid (HA) 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 an anesthetic agent combined with the crosslinked HA component.

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

[0017] In still another embodiment, 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 embodiment, 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 embodiment, the HA component is a gel, for example, a cohesive, hydrated gel. In one embodiment, 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 uncrosslinked HA as

[0024] In still another embodiment, the adjusted pH is above about 7.5. In another embodiment, 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 embodiment, the step of
5 homogenizing comprises subjecting the composition to mixing with a controlled shear.

[0025] In another embodiment, 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
10 another embodiment, the alkaline, free NaHA gel has a pH greater than about 8.0. In still another embodiment the pH is greater than about 10.

[0026] In a further embodiment, 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%.

15 [0027] In still a further embodiment, 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 embodiments, the average size of such particles is at least about 200 μm , and in other embodiments the average size of such particles is at least about 250 μm .

20 [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
25 composition, wherein the anesthetic is lidocaine.

[0029] In a specific embodiment of the ~~invention~~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;
30 crosslinking the free NaHA gel with BDDE to form a crosslinked alkaline HA