A bio-based material composed of fibroin moieties and hyaluronic acid moieties as such is described in PCT/EP2022/066989. There is, however, no teaching that such conjugate is usable in the context of a composition containing botulinum toxin.

In view of the above, it is still an unmet need to provide compositions that have a well-controlled and adjustable release of botulinum toxin while widely avoiding synthetic non-biodegradable moieties such as synthetic linker moieties. The main components of such compositions should preferably be widely biodegradable and/or bio-resorbable. The resources of the solid main components used for preparation of such compositions should preferably be bio-based, thus of biological or biotechnological origin, while optionally synthetic agents such as one or more anesthetics can be comprised. Particularly desirable is an injectable composition usable for treating or preventing a disease or condition associated with hyperactive cholinergic activity, in particular of muscles and/or glands, pain, or for rejuvenation and/or improvement of the skin quality of the face and/or body.

Summary

In an aspect, there is provided a composition comprising or consisting of:

(A) a cross-linked material comprising or consisting of
  (A-i) one or more fibroin moieties, and
  (A-ii) one or more polysaccharide moieties;
  wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties without an interconnecting linker structure;
(B) botulinum toxin;
(C) optionally one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers;
(D) optionally one or more anesthetics; and
(E) optionally one or more further cosmetically and/or pharmaceutically acceptable ingredients different from components (A) to (D).

In another aspect, there is provided a method for preparing a composition as described herein, comprising the steps:

(i) contacting the following components with each other:
  (A-i) one or more fibroin moieties comprising primary amino residues or salts thereof,

(A-ii) one or more polysaccharide moieties comprising carboxylic acid residues or salts thereof,

(A-iii) one or more activating agents that effect reaction of carboxylic acid residues with amino residues thereby forming amide bonds, and

(A-iv) one or more solvents;

(ii) allowing a reaction of at least some of the carboxylic acid residues with at least some of the primary amino residues to form amide bonds conjugating the one or more fibroin moieties covalently with the one or more polysaccharide moieties;

(iii) obtaining cross-linked material (component (A)) from step (ii) and optionally purifying the cross-linked material; and

(iv) adding:
botulinum toxin (component (B)), and
optionally one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers (component (C)), and
optionally one or more anesthetics (component (D)), and/or optionally one or more further cosmetically and/or pharmaceutically acceptable ingredients different from components (A) to (D) (component (E)).

In another aspect, there is provided use of a cross-linked material comprising or consisting of

(A-i) one or more fibroin moieties, and

(A-ii) one or more polysaccharide moieties,

wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties without an interconnecting linker structure,
for retarded and/or controlled release of one or more pharmaceutically and/or cosmetically active agents, in particular botulinum toxin,
preferably wherein the cross-linked material forms a gel a liquid or viscous pharmaceutically acceptable carrier,
in particular wherein the cross-linked material forms part of a composition as described herein is used.

In another aspect, there is provided the composition as described herein for use as a medicament.

In another aspect, there is provided use of the composition as described herein in the manufacture of a medicament for treating or preventing a disease or condition associated with hyperactive cholinergic activity, in particular of muscles and/or glands, and/or pain,

preferably wherein the disease or condition is selected from the group consisting of a motoric disorder, in particular dystonia and/or spasticity, a neuromuscular diseases such as dystonia, spasm, tremor, hyperkinetic movement disorders, and cerebral palsy, pain such as diabetic neuropathy, peripheral neuropathy, neuropathic pain and trigeminal pain, sialorrhea, hyperhidrosis, urological disorders such as detrusor overactivity, neurogenic bladder and interstitial cystitis, treatment of vulvodynia and chronic pelvic pain, prostate disorder such as benign prostate hyperplasia (BPH) and detrusor sphincter dyssynergia (DSD), migraine, neurological disorders such as chronic or episodic migraines, cervical dystonia, post-stroke spasticity, blepharospasm, strabismus, (tension) headaches, pathologically high saliva production, achalasia, sphincter-oddi dysfunction, Hirschsprung's disease, anal fissure, bladder dysfunction such as overactive bladder, a dermatological or aesthetical problem improvable by muscle relaxation, articular pathology, arthritis, and a combination of two or more thereof.

In another aspect, there is provided use of a composition as described herein for cosmetic applications comprising rejuvenation and/or improvement of the skin quality of the face and/or body,

preferably including improving and/or reducing and/or filling and/or preventing wrinkles, in particular of wrinkles resulting from muscular activity such as mimic activity, skin smoothing, improving skin laxity, lifting effect, moisturizing and/or softening the skin, improving and/or reducing and/or filling facial lines, soft-tissue augmentation, improving subdermal support of the brows, malar and buccal fat pads, improving tear troughs, improving nose appearance, resolving facial asymmetries, improving jawlines, or a combination of two or more thereof.

Description

Surprisingly, it has been found that a composition comprising or consisting of a cross-linked material comprising one or more fibroin moieties and one or more polysaccharide moieties, in particular hyaluronic acid moieties, which are covalently conjugated with each other without an interconnecting linker structure can be used in combination with botulinum toxin to provide a composition having desired

properties. Such composition is injectable and usable for treating or preventing a disease or condition associated with hyperactive cholinergic activity, in particular of muscles and/or glands, pain, or for rejuvenation and/or improvement of the skin quality of the face and/or body. Such composition can serve as a biodegradable and bio-resorbable retarded and/or controlled release formulation for botulinum toxin.

A first aspect of the present invention relates to a composition comprising or consisting of:

(A) a cross-linked material comprising or consisting of

(A-i) one or more fibroin moieties, and

(A-ii) one or more polysaccharide moieties;

wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties without an interconnecting linker structure;

(B) botulinum toxin;

Claims

1. A composition comprising or consisting of:
   (A) a cross-linked material comprising or consisting of
      (A-i) one or more fibroin moieties, and
      (A-ii) one or more polysaccharide moieties;
      wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties without an interconnecting linker structure;
   (B) botulinum toxin;
   (C) optionally one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers;
   (D) optionally one or more anesthetics; and
   (E) optionally one or more further cosmetically and/or pharmaceutically acceptable ingredients different from components (A) to (D).

2. The composition of claim 1, wherein the one or more polysaccharide moieties each comprise one or more carboxylic acid residues or salts thereof, preferably wherein the one or more polysaccharide moieties comprise or consist of one or more hyaluronic acid moieties, heparosan moieties, chondroitin sulfate moieties, carboxymethyl cellulose moieties, or a combination of two or more thereof.

3. The composition of any of claims 1 or 2, wherein the one or more polysaccharide moieties are one or more hyaluronic acid moieties.

4. The composition of any of claims 1 to 3, wherein:
   (a) the one or more fibroin moieties have an average molecular weight in the range of at least 5 kDa, preferably 5 to 1000 kDa, in the range of 5 to 400 kDa, in the range of 10 to 400 kDa, or in the range of 100 to 150 kDa, preferably wherein the one or more fibroin moieties are silk fibroin moieties, more preferably silk fibroin moieties having at least

80% sequence homology to a natural insect or spider silk fibroin moiety;

(b) the one or more polysaccharide moieties have an average molecular weight in the range of at least 50 kDa, preferably of 50 to 4000 kDa; and/or

(c) the mass ratio between the components (A-i) : (A-ii) is in the range of 5:1 to 1:20.

5. The composition of any of claims 1 to 4, wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties via amide bonds,
in particular wherein the cross-linked material is further characterized in that it does not comprise:

(a) imide groups;

(b) imine groups;

(c) epoxy groups; and

(d) xenobiotic linker moieties.

6. The composition of any of claims 1 to 5, wherein the botulinum toxin is botulinum neurotoxin serotype A, in particular botulinum neurotoxin serotype A1.

7. The composition of any of claims 1 to 6, wherein the botulinum toxin is not covalently bound with the cross-linked material, and/or
wherein the cross-linked material forms a gel in the liquid or viscous pharmaceutically acceptable carrier, in particular a hydrogel, and the botulinum toxin is dissolved in the liquid or viscous pharmaceutically acceptable carrier soaked in the gel, in particular hydrogel.

8. The composition of any of claims 1 to 7, wherein the composition is an injectable composition comprising or consisting of:

(A) 0.1 to 3.5 % by weight, referred to the composition, of the cross-linked material;

(B) 1 to 150 units/mL, referred to the composition, of botulinum toxin;

(C) 50 to 99.9 % by weight, preferably 59 to 99.9 % by weight, referred to the composition, of one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers;

(D) 0 to 1 % by weight, referred to the composition, one or more anesthetics; and

(E) 0 to 49.9 % by weight, referred to the composition, optionally one or more further cosmetically and/or pharmaceutically acceptable ingredients.

9. The composition of any of claims 1 to 8, wherein the composition comprises at least 50 % by weight, referred to the composition, of a liquid or viscous pharmaceutically acceptable carrier,
preferably wherein the liquid or viscous pharmaceutically acceptable carrier comprises or consists of water, an aqueous buffer, glycerol or a combination of two or more thereof,
in particular wherein the composition is injectable in a soft tissue, in particular injectable intradermally, subdermally, subcutaneously, and/or intramuscularly.

10. The composition of any of claims 1 to 9, wherein the composition is an injectable composition comprising or consisting of:

(A) 0.1 to 3.5 % by weight, referred to the composition, of a cross-linked material comprising or consisting of

(A-i) one or more silk fibroin moieties having an average molecular weight of at least 5 to 400 kDa, and

(A-ii) one or more polysaccharide moieties, in particular hyaluronic acid moieties, having an average molecular weight in the range of 50 to 4000 kDa,

wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties, in particular hyaluronic acid moieties, without an interconnecting linker structure, preferably via amide bonds,
preferably having a mass ratio (A-i) to (A-ii) of 5:1 to 1:20,

(B) 1 to 150 units/mL, referred to the composition, botulinum toxin not covalently bound with the cross-linked material;

(C) 50 to 99.9 % by weight, referred to the composition, of one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers comprising or consisting of water, an aqueous buffer, glycerol or a combination of two or more thereof;

(D) 0 to 1 % by weight, referred to the composition, of one or more anesthetics; and

(E) 0 to 49.9 % by weight, referred to the composition, of one or more further cosmetically and/or pharmaceutically acceptable ingredients different from components (A) to (D).

11. A method for preparing a composition of any one of claims 1 to 10, comprising the steps:

(i) contacting the following components with each other:

(A-i) one or more fibroin moieties comprising primary amino residues or salts thereof,

(A-ii) one or more polysaccharide moieties comprising carboxylic acid residues or salts thereof,

(A-iii) one or more activating agents that effect reaction of carboxylic acid residues with amino residues thereby forming amide bonds, and

(A-iv) one or more solvents;

(ii) allowing a reaction of at least some of the carboxylic acid residues with at least some of the primary amino residues to form amide bonds conjugating the one or more fibroin moieties covalently with the one or more polysaccharide moieties;

(iii) obtaining cross-linked material (component (A)) from step (ii) and optionally purifying the cross-linked material; and

(iv) adding:

botulinum toxin (component (B)), and

optionally one or more liquid or viscous cosmetically and/or pharmaceutically acceptable carriers (component (C)), and optionally one or more anesthetics (component (D)), and/or optionally one or more further cosmetically and/or pharmaceutically acceptable ingredients different from components (A) to (D) (component (E)).

12. Use of a cross-linked material comprising or consisting of

(A-i) one or more fibroin moieties, and

(A-ii) one or more polysaccharide moieties,

wherein the one or more fibroin moieties are covalently conjugated with the one or more polysaccharide moieties without an interconnecting linker structure,

for retarded and/or controlled release of one or more pharmaceutically and/or cosmetically active agents, in particular botulinum toxin,

preferably wherein the cross-linked material forms a gel a liquid or viscous pharmaceutically acceptable carrier,

in particular wherein the cross-linked material forms part of a composition of any one of claims 1 to 10 is used.

13. The composition of any of claims 1 to 10 for use as a medicament.

14. Use of the composition of any of claims 1 to 10 in the manufacture of a medicament for treating or preventing a disease or condition associated with hyperactive cholinergic activity, in particular of muscles and/or glands, and/or pain,

preferably wherein the disease or condition is selected from the group consisting of a motoric disorder, in particular dystonia and/or spasticity, a neuromuscular diseases such as dystonia, spasm, tremor, hyperkinetic movement disorders, and cerebral palsy, pain such as diabetic neuropathy, peripheral neuropathy, neuropathic pain and trigeminal pain, sialorrhea, hyperhidrosis, urological disorders such as detrusor overactivity, neurogenic bladder and interstitial cystitis, treatment of vulvodynia and chronic pelvic pain, prostate disorder such as benign prostate hyperplasia (BPH) and detrusor sphincter dyssynergia (DSD), migraine, neurological disorders such as chronic or episodic migraines, cervical dystonia, post-stroke spasticity, blepharospasm, strabismus, (tension) headaches, pathologically high saliva production, achalasia, sphincter-oddi dysfunction, Hirschsprung's disease, anal fissure, bladder dysfunction such as overactive bladder, a dermatological or aesthetical problem improvable by muscle relaxation, articular pathology, arthritis, and a combination of two or more thereof.

15. Use of a composition of any one or claims 1 to 10 for cosmetic applications comprising rejuvenation and/or improvement of the skin quality of the face and/or body,
preferably including improving and/or reducing and/or filling and/or preventing wrinkles, in particular of wrinkles resulting from muscular activity such as mimic activity, skin smoothing, improving skin laxity, lifting effect, moisturizing and/or softening the skin, improving and/or reducing and/or filling facial lines, soft-tissue augmentation, improving subdermal support of the brows, malar and buccal fat pads, improving tear troughs, improving nose appearance, resolving facial asymmetries, improving jawlines, or a combination of two or more thereof.

16. The use of claim 15, wherein the improvement of the skin quality of the face and/or body comprises the reduction of skin pore size and/or sebum production.

17. The use of claim 15, wherein the rejuvenation comprises the treatment of platysma bands and/or platysma muscles.