SUMMARY

~~In a first aspect, t~~There is provided a hemostatic composition comprising crosslinked gelatin in particulate form suitable for use in hemostasis, wherein the composition is present in paste form containing 15.0 to 19.5% (w/w) crosslinked gelatin, preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and wherein the composition comprises an extrusion enhancer, especially albumin.

In a first aspect, there is provided the use of a hemostatic composition comprising crosslinked gelatin in particulate form in the manufacture of a medicament for the treatment of hemostasis, wherein the composition is present in paste form containing 15.0 to 19.5% (w/w) crosslinked gelatin, preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and wherein the composition comprises an extrusion enhancer, wherein the extrusion enhancer is albumin in an amount of between 0.5 to 5.0% (w/w).

The present disclosure also refers to the use of this hemostatic composition for treating an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue and/or bleeding tissue comprising administering such a hemostatic composition and kits making such a hemostatic composition for the treatment of such injury.

In a second aspect, there is provided the use of the disclosed hemostatic composition ~~for use~~ in the manufacture of a medicament for the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue, bleeding tissue and/or bone defects.

~~In a third aspect, there is provided a use of the disclosed hemostatic composition for the manufacture of a medicament for treating an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue and/or bleeding tissue.~~

In a ~~fourth~~ third aspect, there is provided a kit for making a flowable paste of crosslinked gelatin for the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue and/or bleeding tissue comprising

a) a dry hemostatic composition comprising crosslinked gelatin in particulate form to be reconstituted to a flowable paste containing 15.0 to 19.5% (w/w) crosslinked gelatin, preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and

b) a pharmaceutically acceptable diluent for reconstitution of the hemostatic composition,

wherein either the composition or the diluent comprises albumin in an amount which leads to an albumin concentration in the reconstituted paste of between 0.5 to 5.0% (w/w), preferably 1.0 to 5.0 % (w/w), preferably 2.0 to 4.5% (w/w), more preferred 1.5 to 5.0% (w/w), especially preferred about 1.5% (w/w).

In a ~~fifth~~ fourth aspect, there is provided a method for providing a ready to use form of the disclosed hemostatic composition, wherein the hemostatic composition is provided in a first syringe and a diluent for reconstitution is provided in a second syringe, the first and the second syringe are connected to each other, and the fluid is brought into the first syringe to produce a flowable form of the hemostatic composition; and optionally returning the flowable form of the hemostatic composition to the second syringe at least once.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention provides a hemostatic composition comprising crosslinked gelatin in particulate form suitable for use in hemostasis, wherein the composition is present in paste form containing 15.0 to 19.5% (w/w) crosslinked gelatin (= weight of dry crosslinked gelatin per weight of final composition), preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and wherein the composition comprises an extrusion enhancer.

It has been surprisingly found within the course of the present invention that the provision of extrusion enhancers, such as albumin in the appropriate amount, enables the use of higher gelatin concentrations and that the use of higher gelatin concentrations improves the hemostatic properties of such products. This is an effect which is not suggested in the prior. Moreover, it was surprising that higher concentration of crosslinked gelatin result in better adhesive properties (in contrast to the results known in the prior art (e.g. Fig. 4 of WO2008/076407A2).

For enabling the preferred properties due to the higher gelatin concentrations in the paste according to the present invention, it is necessary to provide the extrusion enhancers in appropriate amounts. The amounts shall be high enough so as to obtain the extrusion effect, i. e. to enable a flowable paste even for amounts of 15 to 19.5% crosslinked gelatin so that the hemostatic composition can be applied e.g. in microsurgery; on the other hand, the amounts shall be as low as to prevent negative functional properties of the hemostatic composition, for example adherence to wounds or hemostatic performance. For example, if the extrusion enhancer is albumin (which is specifically preferred, especially human serum albumin), it must be provided in an amount of between 0.5 to 5.0% (w/w) (= weight of extrusion enhancer per weight of final composition), preferably 1.0 to 5.0 % (w/w), preferably

CLAIMS:

1. Use of a ~~Hemostatic~~ hemostatic composition comprising crosslinked gelatin in particulate form ~~suitable for use in~~ in the manufacture of a medicament for the treatment of hemostasis, wherein the composition is present in paste form containing 15.0 to 19.5% (w/w) crosslinked gelatin, preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and wherein the composition comprises an extrusion enhancer, wherein the extrusion enhancer is albumin in an amount of between 0.5 to 5.0% (w/w).

2. The use of a ~~Hemostatic~~ hemostatic composition according to claim 1, wherein the extrusion enhancer is albumin in an amount of between ~~0.5 to 5.0% (w/w), preferably~~ 1.0 to 5.0 % (w/w), preferably 2.0 to 4.5% (w/w), more preferred 1.5 to 5.0% (w/w), especially preferred about 1.5% (w/w).

3. The use of a ~~Hemostatic~~ hemostatic composition according to claim 1 to 2, wherein the crosslinked gelatin is glutaraldehyde-crosslinked gelatin or genipin-crosslinked gelatin.

4. The use of a ~~Hemostatic~~ hemostatic composition according to any one of claims 1 to 3, wherein the crosslinked gelatin is type B gelatin.

5. The use of a ~~Hemostatic~~ hemostatic composition according to any one of claims 1 to 4, wherein the crosslinked gelatin is present as granular material.

6. The use of a ~~Hemostatic~~ hemostatic composition according to any one of claims 1 to 5, wherein the crosslinked gelatin has a particle size of 100 to 1000µm, preferably 200 to 800µm, most preferred 350 to 550µm.

7. The use of a ~~Hemostatic~~ hemostatic composition according to any one of claims 1 to 6, wherein the composition contains thrombin, preferably 10 to 1000 I.U. thrombin/ml, especially 250 to 700 I.U. thrombin/ml.

8. The use of a ~~Hemostatic~~ hemostatic composition according to any one of claims 1 to 7 ~~for use~~ in the manufacture of a medicament for the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue, bleeding tissue and/or bone defects.

~~9. Use of a hemostatic composition according to any one of claims 1 to 7 for the manufacture of a medicament for treating an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue and/or bleeding tissue.~~

9~~10~~. Kit for making a flowable paste of crosslinked gelatin for the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue and/or bleeding tissue comprising

a) a dry hemostatic composition comprising crosslinked gelatin in particulate form to be reconstituted to a flowable paste containing 15.0 to 19.5% (w/w) crosslinked gelatin, preferably 16.0 to 19.5% (w/w), 16.5 to 19.5% (w/w), 17.0 to 18.5% (w/w) or 17.5 to 18.5% (w/w), more preferred 16.5 to 19.0% (w/w) or 16.8 to 17.8% (w/w), especially preferred 16.5 to 17.5% (w/w), and

b) a pharmaceutically acceptable diluent for reconstitution of the hemostatic composition,

wherein either the composition or the diluent comprises albumin in an amount which leads to an albumin concentration in the reconstituted paste of between 0.5 to 5.0% (w/w), preferably 1.0 to 5.0 % (w/w), preferably 2.0 to 4.5% (w/w), more preferred 1.5 to 5.0% (w/w), especially preferred about 1.5% (w/w).

10~~11~~. Kit according to claim 9~~10~~, wherein the pharmaceutically acceptable diluent comprises a buffer or buffer system, preferably at a pH of 3.0 to 10.0.

11~~12~~. Kit according to claim 9~~10~~ or 10~~11~~, wherein the pharmaceutically acceptable diluent comprises thrombin, preferably 10 to 1000 I.U. thrombin/ml, especially 250 to 700 I.U. thrombin/ml.

12~~13~~. Kit according to any one of claims 9~~10~~ to 11~~12~~, wherein the pharmaceutically acceptable diluent contains a substance selected from the group consisting of NaCl, $CaCl_2$ and sodium acetate.

13~~14~~. Method for providing a ready to use form of a hemostatic composition according to any one of claims 1 to 7, wherein the hemostatic composition is provided in a first syringe and a diluent for reconstitution is provided in a second syringe, the first and the second syringe are connected to each other, and the fluid is brought into the first syringe to produce a flowable form of the hemostatic composition; and optionally returning the flowable form of the hemostatic composition to the second syringe at least once.

14~~15~~. Method according to claim 13~~14~~ wherein the flowable form of the hemostatic composition contains particles that are more than 50% (w/w) with a size of 100 to 1000 µm, preferably more than 80% (w/w) with a size of 100 to 1000 µm.