

Señor Director
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia : Expediente No. **14.114.385**
Asunto : Solicitud de patente: "**COMPOSICIONES HEMOSTÁTICAS**"
Solicitante : BAXTER INTERNATIONAL INC. AND BAXTER
HEALTHCARE SA
Fecha de solicitud : 27 de Mayo de 2014

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **5770** notificado por fijación en lista el 2 de Junio de 2015.

2. Mediante oficio No. **5770** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a la claridad del título, a la presencia de reivindicaciones referentes a un uso o segundo uso, a la presencia de excepciones de patentabilidad, a la claridad del pliego reivindicatorio, a la claridad del capítulo descriptivo, a la novedad de las reivindicaciones 1-7 en vista del documento **D1**: WO9808550 y al nivel inventivo de las reivindicaciones 1-7 y 10-13 en vista de los documentos **D1**: WO9808550, **D2**: US2005284809 y **D3**: US6056970.

3. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

3.1. Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 38 reivindicaciones.

Con el fin de atender a la objeción hecha por el señor examinador, se solicita el cambio de título de la presente solicitud de patente a: **“Composiciones hemostáticas que comprenden gelatina reticulada en forma particulada adecuada para utilizarse en hemostasis”**.

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

- La reivindicación 1 fue modificada de tal manera que se hiciera mayor énfasis en la materia objeto de protección. Por lo tanto, se especificó cuál era el agente de extrusión y las proporciones de los componentes.
- Las reivindicaciones 1, 2, 6, 7, 10 a 12 y 15 contenían modalidades preferidas, ahora se encuentran en reivindicaciones dependientes brindándole mayor claridad al pliego reivindicatorio.
- Con respecto a la objeción realizada a la reivindicación 10 ponemos de presente que el Manual del Examinador establece que los resultados a alcanzar son permitidos, tal y como lo indica en la sección 2.6.5.8, que cumple la función de explicar adicionalmente las partes reclamadas en el paquete.
- Se modificó la reivindicación 11 al especificar el tipo de amortiguador y a limitar el rango del pH.
- En el caso de la reivindicación 13, se adicionaron las concentraciones del NaCl, CaCl y del acetato de sodio.
- Las reivindicaciones 8 y 9 han sido eliminadas del pliego reivindicatorio.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la presencia de excepciones de patentabilidad, reivindicaciones referentes al uso y segundo uso y la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

3.2. Argumentos con respecto a la falta de claridad del Capítulo Descriptivo

Tras las modificaciones realizadas al capítulo reivindicatorio, se considera que la descripción de la presente solicitud cumple con los requerimientos establecidos en el Artículo 28 de la Decisión 486 y que la objeción formulada por el Examinador se ve superada. A continuación se presenta un tabla donde se especifica la página del capítulo descriptivo donde cada reivindicación encuentra soporte:

Reivindicación	Página de la Descripción (Párrafo)
1	2 (1)
2	2,3 (5,2)
3	3(7)
4	3(7)
5	4(3)
6	5(3)
7	8(6)
8	10(2)
9	10(3)
10	10(5)
11	9(2)
12	8,9(6,1)
13	8(5)
14	11(4)
15	12(3)

3.3. Argumentos con respecto a un uso y a un segundo uso

De acuerdo con el Examinador, el uso de la reivindicación 8 no es patentable. A este respecto, se pone de presente que estas reivindicaciones fueron eliminadas del nuevo pliego reivindicatorio. Por lo tanto, las objeciones formuladas por el Examinador en cuanto al uso y al segundo uso se deben tener por superadas. En consecuencia, se

solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

3.4. Argumentos con respecto a la falta de Novedad

De acuerdo al artículo 16 de la Decisión 486, se determina:

***“Artículo 16:** Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica.*

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o en su caso, de la prioridad reconocida”.

La novedad de una invención se evalúa a través de la comparación uno a uno de sus características esenciales. De este modo, una invención puede ser objetada por novedad cuando sus características esenciales son exactamente iguales a las de un antecedente que represente el estado de la técnica conocido al momento de presentar la solicitud. Por lo tanto en caso que llegue a existir al menos una diferencia en dicha comparación, se afirma que la invención SI cumple con el requisito de novedad.

Con base en lo anterior, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos atentamente la reconsideración de las razones por las cuales se objeta la novedad, con base en la siguiente información:

La modificación realizada a la reivindicación 1, con base a las reivindicaciones 1 y 2 originalmente especifica el agente de mejoramiento de extrusión al ser albúmina y menciona las proporciones del componente, materia que no se encuentra revelada en las enseñanzas proporcionadas por el documento D1.

Así, es claro que la materia de invención tal como se encuentra recitada en el nuevo pliego reivindicatorio se debe tener como novedosa, ya que todas las características técnicas esenciales no son anticipadas como un todo por el documento citado D1, por lo que no afectaría la novedad del nuevo capítulo reivindicatorio.

3.5. Argumentos con respecto a la falta de Nivel Inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

Respetuosamente manifestamos que no sería obvia para una persona versada en la materia combinar las enseñanzas de los documentos D1, D2 y D3, toda vez que en los ejemplos de la presente invención es evidente que la consistencia de las pastas de gelatina reticulada contienen mayores cantidades de gelatina reticulada (15 a 18.5% (p/p)) y convincentemente ejemplificada por 17.5% (p/p)) dependiendo de la concentración de albúmina (Figura 2). Un incremento en el contenido de gelatina en el producto Floseal a 17.5%, cuando generalmente el contenido es de aproximadamente 11.14.5%, no mejora la consistencia, como sí lo logra la adición de albúmina como una gente de mejoramiento de extrusión. Estos resultados experimentales demuestran claramente la presencia de un efecto superior en la presente composición, que como sabemos es un claro indicio de presencia de nivel inventivo de acuerdo con el numeral 2.13.5.3.1 de la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELO DE UTILIDAD" de su despacho.

Adicionalmente, ninguno de los documentos citados sugiere el uso de albúmina como un agente de mejoramiento de extrusión que permitiera la presencia de altas concentraciones de gelatina. El señor Examinador menciona que el documento D1 motivaría a una persona versada en la materia a incluir albúmina en las composiciones de dicho documento como un componente bioactivo adicional. Sin embargo, dicho análisis se basó en un análisis retrospectivo o también conocido como "hindsight", el cual lo define el INSTRUCTIVO DE EXÁMENES DE SOLICITUD DE PATENTES DE INVEICÓN Y MODELOS DE UTILIDAD, de la siguiente forma:

Análisis ex post facto o retrospectivo o hindsight

Es importante tener en cuenta que una invención reivindicada que, a primera vista, parece evidente, puede ser inventiva. Una vez formulada una nueva idea, a menudo se puede demostrar teóricamente el modo en el que se podría llegar a ella, a

partir de algo conocido, a través de una serie de etapas aparentemente fáciles. El examinador de patentes debe evitar el uso de un análisis ex post facto de este tipo.

Es decir, el estado de la técnica se debe examinar sin el beneficio del conocimiento ofrecido retrospectivamente por la invención reivindicada. La indicación o la sugerencia que permita llegar a la invención reivindicada deben proceder del estado de la técnica o de los conocimientos generales de la persona del oficio normalmente versada en la materia, y no basarse en la divulgación del solicitante.

La presente solicitud sí tiene nivel inventivo

Como primera medida, mencionamos que los componentes bioactivos incluyen aditivos para mejorar las propiedades biológicas o terapéuticas de una composición, y no se utilizan para impactar las propiedades físicas de la composición como tal. De hecho, como se menciona en D1, las sustancias bioactivas son materiales que han de ser entregados por los hidrogeles, y no materiales que afectan los hidrogeles como tal. Contrario a esto, la albúmina utilizada de acuerdo con la presente invención funciona como una agente de mejoramiento de extrusión específicamente mejorando las propiedades físicas de la composición. Lo que permitiría evidenciar que no se trata de un componente bioactivo como lo afirma el señor Examinador.

Así mismo, el documento D1 menciona los plastificantes como el "glicol polietileno, el sorbitol, el glicerol" (Página 17) como productos que son comúnmente utilizados como lubricantes para mejorar la fluidez del material. Por su parte, la albúmina no es reconocida dentro de dichos ingredientes que pueda facilitar la extrusión de altas concentraciones de gelatina. Finalmente, D1 menciona que los plastificantes y los compuestos bioactivos son materiales diferentes y no incluye a los plastificantes dentro del grupo de compuestos bioactivos. Es decir que D1 menciona los compuestos bioactivos para ser entregados por los hidrogeles de dicha invención, y menciona a los plastificantes como materiales para incrementar la maleabilidad y degradación del gel como tal, donde específicamente menciona a los alcoholes como

plastificantes. Por consiguiente, es evidente que la albúmina no es descrita de ninguna manera por el documento D1, toda vez que tampoco es reconocida como plastificante.

En la producción de la presente invención, se determinó que mayores cantidades de gelatina pueden llegar a ser utilizadas por la adición de una cantidad apropiada de un agente de extrusión de albúmina tal y como se reivindica. Ni este problema, ni su solución, se pueden derivar a partir del documento D1, toda vez que no identifica ni aborda el problema específico causado por concentraciones más altas de gelatina y mucho menos plantea o sugiere la solución actualmente reivindicada.

Por otra parte, la combinación con los documentos D2 o D3 no logra superar esta deficiencia, ya que ninguno de los dos documentos reconoce el efecto de la albúmina e muestra nuevamente una reconstrucción retrospectiva. En D2, la albúmina se cita como "agentes biológicos y hemostáticos" de myriad. Pero no hay ninguna indicación de que existe algún efecto físico, tal como con un mejorador de la extrusión, como sí es reivindicado en la presente invención. Adicionalmente, ninguno de los agentes biológicos y hemostáticos del documento D2 es considerado un agente de mejoramiento de extrusión, a fin de permitir la manipulación de altas cantidades de gelatina en dichas composiciones. Del mismo modo, el documento D3 simplemente analiza la albúmina como un compuesto para ser incluido en una composición hemostática sólida, nuevamente, sin tener en cuenta ningún problema con respecto a la administración de mayores cantidades de gelatina con dicha composición. Este documento no entrega ninguna sugerencia de cualquier impacto físico que podría proporcionar en composiciones con altas cantidades de gelatina.

Por siguiente, es evidente que ninguno de los documentos citados enseña o sugiere el uso de albúmina como un agente de mejoramiento de extrusión para altas cantidades de gelatina con el fin de que dichas composiciones sean utilizables. Esto no podría ser derivado de una manera obvia con base en los documentos citados, dado que no abordan el problema de que al aumentar la concentración de gelatina los productos se vuelven menos fluidos, ni proporcionan ninguna enseñanza para la

inclusión de la albúmina para superar dicho problema y llegar a la solución aquí planteada.

Así, la presente invención es inventiva toda vez que los ejemplos y la descripción tal como fue originalmente presentada muestran claramente la mejora aportada al estado del arte por las composiciones acá reivindicadas en términos de la consistencia de las composiciones que presentan altas cantidades de gelatina. Adicionalmente, es claro al señalar que el efecto (consistencia) de las composiciones acá reivindicadas no podía haber sido esperado por un técnico medio a partir de las enseñanzas de los documentos citados tal como se demostró previamente, en consonancia con los indicios de nivel inventivo que menciona tanto el Manual Andino de Patentes como el "INSTRUCTIVO EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION Y MODELO DE UTILIDAD" de su Despacho, la invención tiene nivel inventivo.

3.6 Concesión de Solicitudes equivalentes

Aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto, informamos a su Despacho que la presente invención ha sido otorgada en la Oficina de Patentes de Europa.

A este respecto, deseamos poner de presente que si bien cada país es autónomo de conceder o negar una solicitud luego de la realización del estudio de fondo, es claro que el hecho de que la novedad y el nivel inventivo de una invención hayan sido reconocidos por varias oficinas a nivel mundial, es un indicio de la patentabilidad de la misma toda vez que (i) el estudio de novedad y nivel inventivo en todas las Oficinas de Patentes del mundo es realizado por personas con conocimientos técnicos en el área de interés que son consideradas personas idóneas para emitir conceptos sobre la patentabilidad de una invención y que (ii) los resultados de los exámenes de novedad o de patentabilidad efectuados respecto a solicitudes extranjeras pueden ser reconocidos

como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención, tal como se señala en el artículo 46 de la Decisión 486:

“Artículo 46.- La oficina nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial.

De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:

a) copia de la solicitud extranjera;

b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;

(...)

*La oficina nacional competente podrá **reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención*** (Negrilla fuera del texto).

3.7 Conclusión

Por todo lo anterior, el documento D1 no resulta anterioridad válida capaz de afectar la novedad de la invención de la presente solicitud. De la misma manera, el documento D1, el documento D2, el documento D3 o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud.

Por lo tanto, consideramos que el Examinador está pasando por alto que una sola diferencia con respecto al estado de la técnica, permite concluir que el objeto reivindicado es nuevo. Además, está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las

enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

4. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 5770, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 38 reivindicaciones.
- Comprobante de pago por 23 reivindicaciones adicionales después de la décima por valor de \$ 736.000.
- Copia de la patente EP 2 771 027 B1.

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

REIVINDICACIONES MODIFICADAS

1. Una composición hemostática que comprende una gelatina reticulada en forma de partículas adecuada para utilizarse en hemostasis, en donde la composición está presente en forma de pasta que contiene del 15.0 al 19.5% (p/p) gelatina reticulada, y en donde, la composición comprende un agente de mejoramiento de extrusión, donde el agente de mejoramiento de extrusión es la albúmina en una proporción entre 0.5 a 5.0% (p/p)
2. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 16 a 19.6% (p/p) de gelatina reticulada.
3. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 16.5 a 19.6% (p/p) de gelatina reticulada.
4. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 17 a 18.5% (p/p) de gelatina reticulada.
5. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 17.5 a 18.6% (p/p) de gelatina reticulada.
6. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 16.5 a 19% (p/p) de gelatina reticulada.
7. La composición hemostática de acuerdo con la reivindicación 1 que comprende del 16.8 a 17.8% (p/p) de gelatina reticulada.
8. La composición hemostática de acuerdo con la

reivindicación 1 que comprende del 16.5 a 17.5% (p/p) de gelatina reticulada.

9. La composición hemostática de acuerdo con las reivindicaciones 1 a 8, caracterizada además porque el agente de mejoramiento de extrusión es albúmina en una cantidad de 1.0 hasta el 5.0% (p/p).
10. La composición hemostática de acuerdo con las reivindicaciones 1 a 8, caracterizada además porque el agente de mejoramiento de extrusión es albúmina en una cantidad de 2.0 hasta el 4.5% (p/p).
11. La composición hemostática de acuerdo con las reivindicaciones 1 a 8, caracterizada además porque el agente de mejoramiento de extrusión es albúmina en una cantidad de 1.5 hasta el 5.0% (p/p).
12. La composición hemostática de acuerdo con las reivindicaciones 1 a 8, caracterizada además porque el agente de mejoramiento de extrusión es albúmina en una cantidad de 1.5% (p/p).
13. La composición hemostática de acuerdo con las reivindicaciones 1 a 12, caracterizada además porque la gelatina reticulada es gelatina reticulada de glutaraldehído o gelatina reticulada de genipina.
14. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 13, caracterizada además porque la gelatina reticulada es gelatina tipo B.
15. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 14, caracterizada además porque la gelatina reticulada está presente como un material en gránulos.
16. La composición hemostática de acuerdo con cualquiera

de las reivindicaciones 1 a 15, caracterizada además porque la gelatina reticulada tiene un tamaño de partícula desde 100 hasta 1000 μm .

17. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 15, caracterizada además porque la gelatina reticulada tiene un tamaño de partícula desde 200 hasta 8000 μm .
18. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 15, caracterizada además porque la gelatina reticulada tiene un tamaño de partícula desde 350 hasta 550 μm .
19. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 18, caracterizada además porque la composición contiene trombina.
20. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 18, caracterizada además porque la composición contiene de 10 a 1000 I.U de trombina/ml.
21. La composición hemostática de acuerdo con cualquiera de las reivindicaciones 1 a 18, caracterizada además porque la composición contiene de 250 a 700 I.U de trombina/ml.
22. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende
 - a) una composición hemostática que comprende una gelatina reticulada en forma de partículas

para ser reconstituida hasta una pasta que puede fluir que contiene del 15.0 al 19.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 0.5 hasta el 5.0% (p/p).

23. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 17.0 al 18.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 0.5 hasta el 5.0% (p/p).

24. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 16.8 al 17.8% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 0.5 hasta el 5.0% (p/p).

25. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 16.5 al 17.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición

hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 0.5 hasta el 5.0% (p/p).

26. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 15.0 al 19.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 2.0 hasta el 4.5% (p/p).

27. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende

una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 17.0 al 18.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 2.0 hasta el 4.5% (p/p).

28. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 16.8 al 17.8% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 2.0 hasta el 4.5% (p/p).

1-7

29. Un paquete para elaborar una pasta que puede fluir de gelatina reticulada para el tratamiento de una lesión seleccionada del grupo que consiste en una herida, una hemorragia, tejido dañado y/o tejido sangrante, que comprende

a) una composición hemostática que comprende una gelatina reticulada en forma de partículas para ser reconstituida hasta una pasta que puede fluir que contiene del 16.5 al 17.5% (p/p) gelatina reticulada, y

b) un diluyente farmacéuticamente aceptable para reconstitución de la composición hemostática, donde dicho diluyente es un medio de rehidratación acuoso, en donde ya sea la composición o el diluyente comprende albúmina en una cantidad que conduce a una concentración de albúmina en la pasta reconstituida de entre el 2.0 hasta el 4.5% (p/p).

30. El paquete tal y como se describe en las reivindicaciones 22 a 29, caracterizado además porque el diluyente farmacéuticamente aceptable comprende un amortiguador o sistema amortiguador, de tal forma que el amortiguador del pH de la composición seca reconstituida sea 6.4 a 7.5.

31. El paquete tal y como se describe en las reivindicaciones 22 a 29, caracterizado además porque el diluyente farmacéuticamente aceptable comprende un amortiguador o sistema amortiguador,

de tal forma que el amortiguador del pH de la composición seca reconstituida sea 6.9 a 7.1.

32. El paquete tal y como se describe en la reivindicación 22 a 31, caracterizado además porque el diluyente farmacéuticamente aceptable comprende trombina.
33. El paquete tal y como se describe en la reivindicación 22 a 31, caracterizado además porque el diluyente farmacéuticamente aceptable comprende 10 a 1000 I.U. de trombina/ml.
34. El paquete tal y como se describe en la reivindicación 22 a 31, caracterizado además porque el diluyente farmacéuticamente aceptable comprende 250 a 700 I.U. de trombina/ml.
35. El paquete tal y como se describe en cualquiera de las reivindicaciones 22 a 34, caracterizado además porque el diluyente farmacéuticamente aceptable contiene una sustancia seleccionada del grupo que consiste en 50 a 200 mM de NaCl, 10 a 80 mM de CaCl_2 y 1 a 50 mM de acetato de sodio.
36. Un método para proporcionar una forma lista para utilizarse de una composición hemostática tal y como se describe en cualquiera de las reivindicaciones 1 a 21, caracterizado además porque la composición hemostática se proporciona en una primera jeringa y un diluyente para reconstitución se proporciona en una segunda jeringa, la primera y segunda jeringas están conectadas entre sí, y el fluido se lleva a la primera jeringa para producir una forma que puede fluir de la composición hemostática; y regresando de manera opcional la forma que puede fluir de la

composición hemostática a la segunda jeringa por lo menos una vez.

37. El método tal y como se describe en la reivindicación 36, caracterizado además porque la forma que puede fluir de la composición hemostática contiene partículas que son de más del 50% (p/p) con un tamaño desde 100 hasta 1000 μm .
38. El método tal y como se describe en la reivindicación 36, caracterizado además porque la forma que puede fluir de la composición hemostática contiene partículas que son de más del 80% (p/p) con un tamaño desde 100 hasta 1000 μm .

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
25 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	32.000.00	800.000.00
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(54) **HEMOSTATIC COMPOSITIONS**
HÄMOSTATISCHE ZUSAMMENSETZUNGEN
COMPOSITIONS HÉMOSTATIQUES

(84) Designated Contracting States: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR (30) Priority: 27.10.2011 US 201161552270 P (43) Date of publication of application: 03.09.2014 Bulletin 2014/36 (73) Proprietors: • Baxter International Inc Deerfield, IL 60015 (US) • Baxter Healthcare SA 8152 Glattpark (Opfikon) (CH)	(72) Inventors: • MCCOY, Jill Sunnyvale, CA 94087 (US) • DWYER, Joseph F. Grayslake, IL 60030 (US) • YANG, Ziping Buffalo Grove, IL 60089 (US) (74) Representative: Sonn & Partner Patentanwälte Riemergasse 14 1010 Wien (AT) (56) References cited: WO-A1-98/08550 WO-A1-03/007845 US-A- 6 066 325 US-A1- 2005 284 809
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Description

FIELD OF THE INVENTION

5 [0001] The present invention relates to hemostatic compositions and processes for making such compositions.

BACKGROUND OF THE INVENTION

10 [0002] Hemostatic compositions in dry storage-stable form that comprise biocompatible, biodegradable, dry stable granular material are known e.g. from WO98/008550A or WO2003/007845A or US 2005/284809 A1. These products have been successfully applied on the art for hemostasis. Floseal® is an example for a highly effective haemostatic agent consisting of a granular gelatin matrix swollen in a thrombin-containing solution to form a flowable paste.

15 [0003] Since such products have to be applied to humans, it is necessary to provide highest safety standards for quality, storage-stability and sterility of the final products and the components thereof. In addition, manufacturing and handling should be made as convenient and efficient as possible.

20 [0004] A successful product in this field (the Floseal® product mentioned above) utilizes a gelatin matrix used in conjugation with a reconstituted lyophilized thrombin solution. The gelatin matrix is applied as a flowable granular form of gelatin and thrombin with a gelatin content of about 11 to 14.5%. Lower gelatin content results in a runny product with diminished performance due to difficulties in having the product remain at the treatment site, especially under conditions of high blood flow. Higher gelatin particle concentration leads to a product that is difficult to deliver by usual means of administration, such as syringes or catheters, due to higher resistance to flow. The inclusion of plasticizers in the composition, e.g., polyethylene glycols, sorbitol, glycerol, and the like has been suggested (EP0927053B1) and can diminish extrusion force, but inclusion of these materials does not necessarily improve performance.

25 [0005] It is an object of the present invention to provide a hemostatic composition based on a crosslinked gelatin with improved adhering and hemostatic properties compared to the gelatin products such as Floseal according to the prior art and methods for making such hemostatic compositions. The compositions should also be provided in a convenient and usable manner, namely as a flowable paste usable in endoscopic surgery and microsurgery. The products must have an extrusion force of 40 N or below, preferably below 35 N, especially preferred below 20 N. The products should preferably be provided in product formats enabling a convenient provision of "ready-to-use" hemostatic compositions, which can be directly applied to an injury without any time consuming reconstitution steps.

SUMMARY OF THE INVENTION

35 [0006] Therefore, 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, 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).

40 [0007] The invention 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.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

45 [0008] 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, wherein the extrusion enhancer is albumin in an amount of between 0.5 to 5.0% (w/w).

50 [0009] 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).

55 [0010] 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. The extrusion enhancer albumin (especially human serum albumin) 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 2.0 to 4.5% (w/w), more preferred 1.5 to 5.0% (w/w), especially preferred about 1.5% (w/w).

[0011] Another class of extrusion enhancers are phospholipids, such as phosphatidylcholine and -serine, or complex mixtures such as lecithins or soy bean oils.

[0012] In another preferred embodiment 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 16.0 to 19.5% (w/w), preferably 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 the extrusion enhancer albumin. Preferably the extrusion enhancer is human serum albumin.

[0013] In another preferred embodiment 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, 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 16.5 to 17.5% (w/w), and wherein the composition comprises an extrusion enhancer in a concentration of more than 0.8% (w/w), preferably about 3.3% (w/w). Preferably the extrusion enhancer is human serum albumin, e.g. in the above mentioned concentrations.

[0014] The hemostatic compositions according to the present invention have specific advantages over the compositions using lower amounts of crosslinked gelatin (13 to 14.5%), especially they have an enhanced in vivo efficacy. It was unexpectedly revealed within the course of the present invention that a formulation with a higher gelatin particle concentration results in greater hemostatic performance both in ex vivo test methods that use whole human blood and in pre-clinical animal experiments. The products according to the present invention enable a reduced surgical approximation time and a faster time to hemostasis.

[0015] The compositions according to the present invention have a mean extrusion force (employing the test method described in example 1) of 40 N or below, preferably below 35 N, especially preferred below 20 N.

[0016] According to preferred embodiment of the present invention, the hemostatic composition comprises glutaraldehyde-crosslinked gelatin or genipin (Methyl (1R,2R,6S)-2-hydroxy-9-(hydroxymethyl)-3-oxabicyclo[4.3.0]nona-4,8-diene-5-carboxylate)-crosslinked gelatin, preferably type B gelatin, more preferably type B gelatin of hide origin.

[0017] Preferably, the crosslinked gelatin is present as granular material.

[0018] The hemostatic composition according to the present invention preferably comprises a gelatin polymer which is especially a type B gelatin polymer. Type B gelatin has proven to be specifically advantageous for use in hemostatic agents as the base treatment is highly effective in generating gelatin of appropriate properties and in mitigating risk of viral and zoonotic infection. A specifically preferred gelatin preparation can be prepared by processing young bovine corium with 2 N NaOH for about 1 hour at room temperature, neutralizing to pH 7-8, and heating to 70°C. The corium is then fully solubilized to gelatin with 3-10% (w/w), preferably 7-10% (w/w) gelatin in solution. This solution can be cast, dried and ground to provide gelatin type B powder.

[0019] Preferably, the gelatin has a Bloom strength of 200 to 400, especially a type B gelatin with a Bloom strength of 200 to 400. Bloom is a test to measure the strength of gelatin. The test determines the weight (in grams) needed by a probe (normally with a diameter of 0.5 inch) to deflect the surface of the gel 4 mm without breaking it. The result is expressed in Bloom (grades). To perform the Bloom test on gelatin, a 6.67% gelatin solution is kept for 17-18 hours at 10°C prior to being tested.

[0020] The hemostatic composition according to the present invention preferably contains the crosslinked gelatin in particulate form, especially as granular material. This granular material can rapidly swell when exposed to a fluid (i.e. the diluent) and in this swollen form is capable of contributing to a flowable paste that can be applied to a bleeding site. According to a preferred embodiment, the crosslinked gelatin is provided from a dry crosslinked gelatin. This dry crosslinked gelatin powder can be prepared to re-hydrate rapidly if contacted with a pharmaceutically acceptable diluent. The gelatin granules, especially in the form of a gelatin powder, preferably comprise relatively large particles, also referred to as fragments or subunits, as described in WO98/08550A and WO2003/007845A. A preferred (median) particle size will be the range from 10 to 1.000 µm, preferably from 200 to 800 µm, but particle sizes outside of this preferred range may find use in many circumstances.

[0021] Usually, the gelatin particles have a mean particle diameter ("mean particle diameter" is the median size as measured by laser diffractometry; "median size" (or mass median particle diameter) is the particle diameter that divides the frequency distribution in half; fifty percent of the particles of a given preparation have a larger diameter, and fifty percent of the particles have a smaller diameter) from 10 to 1000 µm, preferably 50 to 700 µm, 200 to 700 µm, 300 to 550 µm, especially preferred 350 to 550 µm (median size). Although the terms powder and granular (or granulates) are

sometimes used to distinguish separate classes of material, powders are defined herein as a special sub-class of granular materials. In particular, powders refer to those granular materials that have the finer grain sizes, and that therefore have a greater tendency to form clumps when flowing. Granules include coarser granular materials that do not tend to form clumps except when wet.

[0022] The present crosslinked gelatin in particulate form suitable for use in hemostasis may include dimensionally isotropic or non-isotropic forms. For example, the crosslinked gelatin in the kit according to the present invention may be granules or fibers; and may be present in discontinuous structures, for example in powder forms.

[0023] The dry gelatin composition is liquid absorbing. For example, upon contact with liquids, e.g. aqueous solutions or suspensions (especially a buffer or blood) the crosslinked gelatin takes up the liquid and will display a degree of swelling, depending on the extent of hydration. The material preferably absorbs from at least 400 %, preferably about 500% to about 2000%, especially from about 500% to about 1300% water or aqueous buffer by weight, corresponding to a nominal increase in diameter or width of an individual particle of subunit in the range from e.g. approximately 50% to approximately 500%, usually from approximately 50% to approximately 250%. For example, if the (dry) granular particles have a preferred size range of 0.01 mm to 1.5 mm, especially of 0.05 mm to 1 mm, the fully hydrated composition (e.g. after administration on a wound or after contact with an aqueous buffer solution) may have a size range of 0.05 mm to 3 mm, especially of 0.25 mm to 1.5 mm.

[0024] The dry compositions will also display a significant "equilibrium swell" when exposed to an aqueous re-hydrating medium (= pharmaceutically acceptable diluent, also referred to as reconstitution medium). Preferably, the swell will be in the range from 400% to 1300%, preferably 400% to 1000%, more preferred 500% to 1100%, especially preferred from 500% to 900%, depending on its intended use. Such equilibrium swell may be controlled e.g. (for a crosslinked polymer) by varying the degree of cross-linking, which in turn is achieved by varying the cross-linking conditions, such as the duration of exposure of a cross-linking agent, concentration of a cross-linking agent, cross-linking temperature, and the like. Materials having differing equilibrium swell values perform differently in different applications. The ability to control crosslinking and equilibrium swell allows the compositions of the present invention to be optimized for a variety of uses. In addition to equilibrium swell, it is also important to control the hydration of the material immediately prior to delivery to a target site. Hydration and equilibrium swell are, of course, intimately connected. A material with 0% hydration will be non-swollen. A material with 100% hydration will be at its equilibrium water content. Hydrations between 0% and 100% will correspond to swelling between the minimum and maximum amounts. "Equilibrium swell" may be determined by subtracting the dry weight of the gelatin hydrogel powder from its weight when fully hydrated and thus fully swelled. The difference is then divided by the dry weight and multiplied by 100 to give the measure of swelling. The dry weight should be measured after exposure of the material to an elevated temperature for a time sufficient to remove substantially all residual moisture, e.g., two hours at 120°C. The equilibrium hydration of the material can be achieved by immersing the dry material in a pharmaceutically acceptable diluent, such as aqueous saline, for a time period sufficient for the water content to become constant, typically for from 18 to 24 hours at room temperature.

[0025] The crosslinked gelatin may be provided as a film which can then be milled to form a granular material. Most of the particles contained in a granular material (e.g. more than 90% w/w) have preferably particle sizes of 10 to 1.000 μm , preferably 50 to 700 μm , 200 to 700 μm , 300 to 550 μm , especially preferred 350 to 550 μm .

[0026] Preferably, 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 .

[0027] Examples of suitable gelatin materials for crosslinking are described i.a. in examples 1 and 2 of EP1803417B1 and example 14 of US6,066,325A and US6,063,061A. Gelatin may also be used with processing aids, such as PVP, PEG and/or dextran as re-hydration aids.

[0028] In one particular aspect of the present invention, compositions will comprise crosslinked gelatin powders having a moisture content of 20% (w/w) or less, wherein the powder was crosslinked in the presence of a re-hydration aid so that the powder has an aqueous re-hydration rate which is at least 5% higher than the re-hydration rate of a similar powder prepared without the re-hydration aid. The "re-hydration rate" is defined according to EP1803417B1 to mean the quantity of an aqueous solution, typically 0.9% (w/w) saline that is absorbed by a gram of the powder (dry weight basis) within thirty seconds, expressed as g/g. The rehydration rate is measured by mixing the crosslinked gelatin with saline solution for 30 seconds and depositing the wet gelatin on a filter membrane under vacuum to remove the free aqueous solution. One then records the weight of the wet gelatin retained on the filter, dries it (e.g. 2 hr at 120°C), then records the dry weight of the gelatin and calculates the weight of solution that was absorbed per gram of dry gelatin.

[0029] Preferred compositions of the present invention will have a re-hydration rate of at least 3 g/g, preferably at least 3.5 g/g, and often 3.75 g/g or higher. Re-hydration rates of similar powders prepared without the re-hydration aids are typically below three, and a percentage increase in re-hydration rate will usually be at least 5%, preferably being at least 10%, and more preferably being at least 25% or higher.

[0030] Crosslinking can be done with any suitable crosslinker, e.g. glutaraldehyde such as e.g. described in WO98/08550A and WO2003/007845A. Crosslinking can also be carried out with a non-toxic crosslinker such as genipin and the like.

[0031] Production cost is less for a genipin crosslinked gelatin product according to the present invention than a glutaraldehyde crosslinked one, since reagent, energy, and time costs are lower. The genipin crosslinked gelatin reaction can be performed in water at neutral pH at room temperature for ≤ 16 hours. The product can be cleaned-up by an ethanol and/or water wash which is not only cheaper, but more importantly, safer for the operator.

[0032] The method preferably applies the gelatin as being present in dry form before the crosslinking step.

[0033] The preferred genipin-type crosslinker according to the present invention is, of course, genipin (Methyl (1*R*,2*R*,6*S*)-2-hydroxy-9-(hydroxymethyl)-3-oxabicyclo[4.3.0]nona-4,8-diene-5-carboxylate); however, also other crosslinkers of the iridoid- or secoiridoid-type may be used, such as oleuropein. Preferred concentrations of genipin for crosslinking are in the range of 0.5 to 20 mM, preferably 1 to 15 mM, especially 2 to 10 mM.

[0034] According to a preferred embodiment of the present invention, the genipin crosslinked gelatin is subjected to a quenching/oxidation step with oxidizing agents such as bleach, tBu-hydroperoxide, etc., preferably to a treatment with sodium percarbonate, sodium hypochlorite, chlorine water or hydrogen peroxide (H_2O_2), especially preferred is a treatment with sodium percarbonate or H_2O_2 most preferred is a treatment with percarbonate.

[0035] Preferred H_2O_2 concentrations are 0.5 to 20% (w/w), especially 1 to 15% (w/w), more preferred about 5 % (w/w). In an especially preferred embodiment the genipin concentration is between 5 to 10 mM, the reaction time of gelatin with genipin is between 3 to 10 hours, especially 6 hours, the H_2O_2 concentration is between 3 to 5 % (w/w) and the reaction time of the genipin-crosslinked gelatin with H_2O_2 is about 20 hours.

[0036] Preferred percarbonate concentrations are between 1 to 10 % (w/w), especially 1 to 5 % (w/w), more preferred 1 to 4 % (w/w). In an especially preferred embodiment the genipin concentration is between 5 to 10 mM (especially about 8 mM), the reaction time of gelatin with genipin is between 3 to 10 hours (especially about 5 hours), the percarbonate concentration is between 1 to 10 % (w/w), especially preferred between 1 to 4 % w/w, and the reaction time of the genipin-crosslinked gelatin with percarbonate is between 1 to 20 hours, preferably between 1 to 5 hours (e.g. 1, 2 or 3 hours).

Quenching may also be carried out in presence of antioxidants such as sodium ascorbate or by controlling oxidation potential of the reaction environment such as carrying out quenching and/or genipin reaction in an inert atmosphere such as nitrogen or argon.

[0037] Preferred crosslinking reaction conditions include the performance in aqueous solution, preferably in a phosphate buffered saline (PBS)/ethanol buffer, especially at a pH of 4 to 12, preferably of 5.0 to 10.0, especially of 6 to 8, or in deionized water or other aqueous buffers which may contain between 0 to 50% of a water miscible organic solvent. A PBS buffer contains physiological amounts of NaCl and KCl in a phosphate buffer at a physiological pH. An example for a PBS buffer contains 137 mM NaCl, 2.7 mM KCl, 10 mM $Na_2HPO_4 \cdot 2 H_2O$, 1.76 mM KH_2PO_4 (pH = 7.4). Another example of a PBS buffer consists of 137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2HPO_4 and 1.4 mM KH_2PO_4 (pH = 7.5).

[0038] The reaction may also be carried out in an aqueous buffer containing up to 50% of a water-miscible organic solvent and/or processing aids such as PEG, PVP, mannitol, sodium percarbonate, sodium lactate, sodium citrate, sodium ascorbate etc..

[0039] Preferably, the crosslinking step is performed at a temperature of 4°C to 45°C, preferably of 15 to 45°C, especially of 20 to 40°C.

[0040] The crosslinking step may be followed by a quenching step, especially with an amino-group containing quencher, preferably an amino acid, especially glycine. With the quencher, yet unreacted genipin-type crosslinkers are inactivated (e.g. by reaction with the quencher in excess) to prevent further crosslinking. Quenching may also be carried out by raising pH of solution to between 8 to 14, or by using nucleophilic compounds containing amino, thiol, or hydroxyl groups and also a combination of pH raising and using nucleophilic compounds. The quenching step after the genipin-gelatin crosslinking reaction according to the present invention can be actively directed to impart desired physical performance such as swell and TEG which are important determinants of hemostatic activity above and beyond the general genipin-crosslinking alone.

[0041] The crosslinked gelatin is preferably washed after the crosslinking step, preferably by methanol, ethanol or water, especially by deionized water. Another preferred washing step applies an aqueous buffer containing up to 50% (v/v) of water-miscible organic solvent and/or one or more processing aids.

[0042] According to a preferred embodiment, the crosslinked gelatin is dried. In such a dried state, the hemostatic composition is storage-stable for long time even at elevated temperatures (e.g. more than 20°C, more than 30°C or even more than 40°C). Preferred dryness conditions include crosslinked biocompatible polymers which are dried to have a moisture content of below 15% (w/w), preferably below 10%, more preferred below 5%, especially below 1%. In another preferred embodiment the product may be supplied in a hydrated or wet state where the hydrating solution may be a biocompatible buffer or solution. A Glu-Gel product has a tendency to be camouflaged by surrounding tissue, since it's slightly yellow color blends in with it. This makes visual evaluation of the desired application problematic. The genipin crosslinked gelatin products according to the present invention appear variable color from pale yellow to dark blue or green based upon degree of crosslinking reaction conditions, and subsequent processing and finishing steps. This tunability of color and ability to obtain desired color in finished product color has the added advantage of providing

physicians visual indication of proper product application in wound sites, since this color differentiates it from surrounding tissue, instead of potentially being camouflaged by it. This is another novel feature of this invention. On the other hand, the color can be removed to obtain a non-colored product, depending on the needs with respect to the final products.

[0043] In a preferred embodiment the biocompatible polymer, e.g. gelatin, crosslinked with a genipin-type crosslinker, e.g. genipin, is a homogeneously (uniformly) crosslinked polymer as can be shown e.g. by fluorescence measurements as described in Example 3 of the present application. In an especially preferred embodiment the biocompatible polymer, such as gelatin, is present as a homogeneously genipin crosslinked biocompatible polymer, such as gelatin, in particulate form.

[0044] A hemostatic composition according to the present invention is preferred, wherein excipients, such as lubricants, e.g. hyaluronic acid, are present.

[0045] In another embodiment of the present invention excipients, such as lubricants, e.g. hyaluronic acid, are excluded.

[0046] The pharmaceutically acceptable diluent is preferably an aqueous solution and may contain a substance selected from the group consisting of NaCl, CaCl₂ and sodium acetate. For example, a pharmaceutically acceptable diluent comprises water for injection, and - independently of each other - 50 to 200 mM NaCl (preferably 150 mM), 10 to 80 mM CaCl₂ (preferably 40 mM) and 1 to 50 mM sodium acetate (preferably 20 mM). In another embodiment the pharmaceutically acceptable diluent contains less than 35 g/l of mannitol, preferably less than 25 g/l, more preferred less than 10 g/l, especially preferred the pharmaceutically acceptable diluent is essentially free of mannitol.

[0047] According to a preferred embodiment, the pharmaceutically acceptable diluent comprises thrombin, preferably 10 to 1000 I.U. thrombin/ml, especially 250 to 700 I.U. thrombin/ml. Preferably, the hemostatic composition in this ready to use form contains 10 to 100.000 International Units (I.U.) of thrombin, more preferred 100 to 10.000 I.U., especially 500 to 5.000 I.U.. Thrombin (or any other coagulation inducing agent, such as snake venom, a platelet activator, a thrombin receptor activating peptide and a fibrinogen precipitating agent) can be derived from any thrombin preparation which is suitable for use in humans (i.e. pharmaceutically acceptable). Suitable sources of thrombin include human and bovine blood, plasma or serum (thrombin of other animal sources can be applied if no adverse immune reactions are anticipated), thrombin of recombinant origin (e.g. human recombinant thrombin) and autologous human thrombin can be preferred for some applications.

[0048] The pharmaceutically acceptable diluent is used in an amount to achieve the desired end-concentration in the ready-to-use composition. The thrombin preparation may contain other useful component, such as ions, buffers, excipients, stabilizers, etc.. Preferably, the thrombin preparation contains human albumin as the extrusion enhancer. Preferred salts are NaCl and/or CaCl₂, both used in the usual amounts and concentrations applied for thrombin (e.g. 0.5 to 1.5 % NaCl (e.g. 0.9%) and/or 20 to 80 mM CaCl₂ (e.g. 40 mM)).

In a further embodiment, the diluent can also include a buffer or buffer system so as to buffer the pH of the reconstituted dry composition, preferably at a pH of 3.0 to 10.0, more preferred of 6.4 to 7.5, especially at a pH of 6.9 to 7.1.

[0049] Establishment of appropriate amounts of crosslinked gelatin, diluent and extrusion enhancer may be made in the kit according to the aforementioned prerequisites: For example a) a vial with 0.736 to 0.995 g dry crosslinked gelatin (corresponding to 15.0 to 19.5% (w/w) in the final product) may be provided and b) a second vial with 4 ml diluent with 60 to 240 mg albumin and, optionally, thrombin at a concentration of 500 I.U./ml and/or 40 mM CaCl₂. Alternatively, albumin may be added in lyophilized form to the dry gelatin component a) of the kit. For example, a) a vial with 0.573 to 0.775 g dry crosslinked gelatin (corresponding to 15.0 to 19.5% (w/w) in the final product) thereof 48 to 192 mg albumin may be provided and b) a second vial with 3.2 ml diluent and, optionally, thrombin at a concentration of 500 I.U./ml and/or 40 mM CaCl₂.

[0050] The crosslinked gelatin component of the kit according to the present invention is preferably provided as a dry composition, wherein the crosslinked gelatin is present in dry form.

[0051] A substantially dry crosslinked gelatin composition according to the present invention has a residual content of moisture which may approximately correspond to the moisture content of comparable available products, such as Floseal® (Floseal, for example, has approximately 8-12% moisture as a dry product).

[0052] The dry crosslinked gelatin in particulate form suitable for use in hemostasis in the kit according to the present invention is preferably gelatin in powder form, especially wherein the powder particles have a median particle size of 10 to 1000 µm, preferably 50 to 700 µm, 200 to 700 µm, 300 to 550 µm, especially preferred 350 to 550 µm. A "dry granular preparation of crosslinked gelatin" according to the present invention is in principle known e.g. from WO98/08550A. Preferably, the crosslinked gelatin is a biocompatible, biodegradable dry stable granular material.

[0053] According to another aspect, the present invention relates to a hemostatic composition according to the present invention for use in the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue, bleeding tissue and/or bone defects.

[0054] According to another aspect, the present description also provides a method for delivering a hemostatic composition according to the invention to a target site in a patient's body, said method comprising delivering a hemostatic composition produced by the process according to the present invention to the target site. Although also the dry composition can be directly applied to the target site (and, optionally be contacted with a diluent at the target site, if necessary),

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it is preferred to contact the dry hemostatic composition with a pharmaceutically acceptable diluent before administration to the target site, so as to obtain a hemostatic composition according to the present invention in paste form.

[0055] In such a method, 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, may be applied, this kit 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 (= weight of dry gelatin to 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), crosslinked gelatin and
- b) a pharmaceutically acceptable diluent for reconstitution of the hemostatic composition, wherein either the composition or the diluent comprises the extrusion enhancer albumin in an amount which leads to an albumin concentration in the reconstituted paste 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 2.0 to 4.5% (w/w), more preferred 1.5 to 5.0% (w/w), especially preferred about 1.5% (w/w).

[0056] A preferred further component of such a kit is - specifically if the hemostatic composition is contained in dry form - a diluent for reconstitution (= re-hydration medium) of the hemostatic composition. Further components of the kit may be administration means, such as syringes, catheters, brushes, etc. (if the compositions are not already provided in the administration means) or other components necessary for use in medical (surgical) practice, such as substitute needles or catheters, extra vials or further wound cover means. Preferably, the kit according to the present invention comprises a syringe housing the dry and stable hemostatic composition and a syringe containing the diluent (or provided to take up the diluent from another diluent container).

[0057] In a preferred embodiment, the pharmaceutically acceptable diluent is provided in a separate container. This can preferably be a syringe. The diluent in the syringe can then easily be applied to the final container for reconstitution of the dry hemostatic compositions according to the present invention. If the final container is also a syringe, both syringes can be finished together in a pack. It is therefore preferred to provide the dry hemostatic compositions according to the present invention in a syringe which is finished with a diluent syringe with a pharmaceutically acceptable diluent for reconstituting said dry and stable hemostatic composition.

[0058] According to a preferred embodiment, the final container further contains an amount of a stabilizer effective to inhibit modification of the polymer when exposed to the sterilizing radiation, preferably ascorbic acid, sodium ascorbate, other salts of ascorbic acid, or an antioxidant.

[0059] With such a pharmaceutically acceptable diluent, a ready to use form of the present hemostatic composition may be provided which can then be directly applied to the patient. Accordingly, also method for providing a ready to use form of a hemostatic composition according to the present invention is provided, 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. Preferably, the ready-to use preparations are present or provided as hydrogels. Products of this kind are known in principle in the art, yet in a different format. Therefore, a method for providing a ready to use form of a hemostatic composition according to the present invention, 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 diluent 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, is a preferred embodiment of the present invention. This process (also referred to as "swooshing") provides a suitable ready-to-use form of the compositions according to the present invention which can easily and efficiently be made also within short times, e.g. in emergency situations during surgery. This flowable form of the hemostatic composition provided by such a method is specifically suitable for use in the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue, bleeding tissue and/or bone defects.

[0060] For stability reasons, such products (as well as the products according to the present invention) are usually provided in a dry form in a final container and brought into the ready-to-use form (which is usually in the form of a (hydro)gel, suspension or solution) immediately before use, necessitating the addition of a pharmaceutically acceptable diluents (= re-hydration medium).

[0061] According to another aspect, the present invention relates to a method for providing a ready to use form of a hemostatic composition according to the present invention, 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.

[0062] Preferably, the flowable form of the hemostatic composition according to the present invention contains more than 50% (w/w) particles with a size of 100 to 1000 μm , preferably more than 80% (w/w) particles with a size of 100 to 1000 μm .

[0063] The biocompatible hemostatic crosslinked polymer according to the present invention - once applied to a wound - forms an efficient matrix which can form a barrier for blood flow. Specifically the swelling properties of the hemostatic polymer can make it an effective mechanical barrier against bleeding and re-bleeding processes.

[0064] The present composition may additionally contain a hydrophilic polymeric component (also referred to as "reactive hydrophilic component" or "hydrophilic (polymeric) crosslinker") which further enhances the adhesive properties of the present composition. This hydrophilic polymeric component of the haemostatic composition according to the present invention acts as a hydrophilic crosslinker which is able to react with its reactive groups once the haemostatic composition is applied to a patient (e.g. to a wound of a patient or another place where the patient is in need of a hemostatic activity). Therefore it is important for the present invention that the reactive groups of the hydrophilic polymeric component are reactive when applied to the patient. It is therefore necessary to manufacture the haemostatic composition according to the present invention so that the reactive groups of the polymeric component which should react once they are applied to a wound are retained during the manufacturing process.

[0065] For hydrophilic polymeric crosslinkers whose reactive groups are hydrolysable, premature contact with water or aqueous liquids has to be prevented before administration of the haemostatic composition to the patient, especially during manufacture. However, processing of the hydrophilic polymeric component during manufacturing may be possible also in an aqueous medium at conditions where the reactions of the reactive groups are inhibited (e.g. at a low pH). If the hydrophilic polymeric components can be melted, the melted hydrophilic polymeric components can be sprayed or printed onto the matrix of crosslinked gelatin. It is also possible to mix a dry form (e.g. a powder) of the hydrophilic polymeric component with a dry form of the crosslinked gelatin. If necessary, then an increase of the temperature can be applied to melt the sprinkled hydrophilic polymeric component to the crosslinked gelatin to achieve a permanent coating of the haemostatic composition. Alternatively, these hydrophilic polymeric components can be taken up into inert organic solvents (inert vis-a-vis the reactive groups of the hydrophilic polymeric components) and brought onto the matrix of the crosslinked gelatin. Examples of such organic solvents are dry ethanol, dry acetone or dry dichloromethane (which are e.g. inert for hydrophilic polymeric components, such as NHS-ester substituted PEGs). Alternatively, nucleophilic groups may also be added (e.g. PEG-SH).

[0066] In a preferred embodiment the hydrophilic polymer component is a single hydrophilic polymer component and is a polyalkylene oxide polymer, preferably a PEG comprising polymer. The reactive groups of this reactive polymer are preferably electrophilic groups.

[0067] The reactive hydrophilic component may be a multi-electrophilic polyalkylene oxide polymer, e.g. a multi-electrophilic PEG. The reactive hydrophilic component can include two or more electrophilic groups, preferably a PEG comprising two or more reactive groups selected from succinimidylesters ($-\text{CON}(\text{COCH}_2)_2$), aldehydes ($-\text{CHO}$) and isocyanates ($-\text{N}=\text{C}=\text{O}$), e.g. a component as disclosed in the WO2008/016983 A.

[0068] Preferred electrophilic groups of the hydrophilic polymeric crosslinker according to the present invention are groups reactive to the amino-, carboxy-, thiol- and hydroxy- groups of proteins, or mixtures thereof.

[0069] Preferred amino group-specific reactive groups are NHS-ester groups, imidoester groups, aldehyde-groups, carboxy-groups in the presence of carbodiimides, isocyanates, or THPP (beta-[Tris(hydroxymethyl)phosphino] propionic acid), especially preferred is Pentaerythritolpoly(ethyleneglycol)ether tetrasuccinimidyl glutarate (= Pentaerythritol tetrakis[1-1'-oxo-5'-succinimidylpentanoate-2-poly-oxoethyleneglycole]ether (= an NHS-PEG with MW 10,000).

[0070] Preferred carboxy-group specific reactive groups are amino-groups in the presence of carbodiimides.

[0071] Preferred thiol group-specific reactive groups are maleimides or haloacetyls.

[0072] Preferred hydroxy group-specific reactive group is the isocyanate group.

The reactive groups on the hydrophilic cross-linker may be identical (homo-functional) or different (hetero-functional). The hydrophilic polymeric component can have two reactive groups (homo-bifunctional or hetero-bifunctional) or more (homo/hetero-trifunctional or more).

[0073] In special embodiments the material is a synthetic polymer, preferably comprising PEG. The polymer can be a derivative of PEG comprising active side groups suitable for cross-linking and adherence to a tissue.

[0074] By the reactive groups the hydrophilic reactive polymer has the ability to cross-link blood proteins and also tissue surface proteins. Cross-linking to the crosslinked gelatin is also possible.

[0075] The multi-electrophilic polyalkylene oxide may include two or more succinimidyl groups. The multi-electrophilic polyalkylene oxide may include two or more maleimidyl groups.

[0076] Preferably, the multi-electrophilic polyalkylene oxide is a polyethylene glycol or a derivative thereof.

[0077] In a most preferred embodiment the hydrophilic polymeric component is pentaerythritolpoly(ethyleneglycol)ether tetrasuccinimidyl glutarate (=COH102, also pentaerythritol tetrakis[1-1'-oxo-5'-succinimidylpentanoate-2-poly-oxoethyleneglycole]ether).

[0078] The hydrophilic polymeric component is a hydrophilic crosslinker. According to a preferred embodiment, this

crosslinker has more than two reactive groups for crosslinking ("arms"), for example three, four, five, six, seven, eight, or more arms with reactive groups for crosslinking. For example, NHS-PEG-NHS is an effective hydrophilic crosslinker according to the present invention. However, for some embodiments, a 4-arm polymer (e.g. 4-arms-p-NP-PEG) may be more preferred; based on the same rationale, an 8-arm polymer (e.g. 8-arms-NHS-PEG) may even be more preferred for those embodiments where multi-reactive crosslinking is beneficial. Moreover, the hydrophilic crosslinker is a polymer, i.e. a large molecule (macromolecule) composed of repeating structural units which are typically connected by covalent chemical bonds. The hydrophilic polymer component should have a molecular weight of at least 1000 Da (to properly serve as crosslinker in the hemostatic composition according to the present invention); preferably the crosslinking polymers according to the present invention has a molecular weight of at least 5000 Da, especially of at least 8000 Da.

[0079] For some hydrophilic crosslinkers, the presence of basic reaction conditions (e.g. at the administration site) is preferred or necessary for functional performance (e.g. for a faster cross-linking reaction at the administration site). For example, carbonate or bicarbonate ions (e.g. as a buffer with a pH of 7.6 or above, preferably of 8.0 or above, especially of 8.3 and above) may be additionally provided at the site of administration (e.g. as a buffer solution or as a fabric or pad soaked with such a buffer), so as to allow an improved performance of the hemostatic composition according to the present invention or to allow efficient use as a hemostatic and/or wound adherent material.

[0080] The reactivity of the hydrophilic polymeric component (which, as mentioned, acts as a crosslinker) in the composition according to the present invention is retained in the composition. This means that the reactive groups of the crosslinker have not yet reacted with the haemostatic composition and are not hydrolyzed by water (or at least not in a significant amount which has negative consequences on the hemostatic functionality of the present compositions). This can be achieved by combining the crosslinked gelatin with the hydrophilic crosslinker in a way which does not lead to reaction of the reactive groups of the crosslinker with the hemostatic polymer or with water. Usually, this includes the omitting of aqueous conditions (or wetting), especially wetting without the presence of acidic conditions (if crosslinkers are not reactive under acidic conditions). This allows the provision of reactive haemostatic materials.

[0081] Preferred ratios of the crosslinked gelatin to hydrophilic polymeric component in the hemostatic composition according to the present invention are from 0.1 to 50% (w/w), preferably from 5 to 40% (w/w).

[0082] Further components may be present in the hemostatic composition according to the present invention. According to preferred embodiments, the hemostatic compositions according to the present invention may further comprise a substance selected from the group consisting of antifibrinolytic, procoagulant, platelet activator, antibiotic, vasoconstrictor, dye, growth factors, bone morphogenetic proteins and pain killers.

[0083] The present invention also refers to a finished final container containing the hemostatic composition according to the present invention. This finished container contains the hemostatic composition according to the present invention in a sterile, storage-stable and marketable form. The final container can be any container suitable for housing (and storing) pharmaceutically administrable compounds. Syringes, vials, tubes, etc. can be used; however, providing the hemostatic compositions according to the present invention in a syringe is specifically preferred. Syringes have been a preferred administration means for hemostatic compositions as disclosed in the prior art also because of the handling advantages of syringes in medical practice. The compositions may then preferably be applied (after reconstitution) via specific needles of the syringe or via suitable catheters. The reconstituted hemostatic compositions (which are preferably reconstituted to form a hydrogel) may also be applied by various other means e.g. by a spatula, a brush, a spray, manually by pressure, or by any other conventional technique. Administration of the reconstituted hemostatic composition to a patient by endoscopic (laparoscopic) means is specifically preferred. Usually, the reconstituted hemostatic compositions according to the present invention will be applied using a syringe or similar applicator capable of extruding the reconstituted composition through an orifice, aperture, needle, tube, or other passage to form a bead, layer, or similar portion of material. Mechanical disruption of the compositions can be performed by extrusion through an orifice in the syringe or other applicator, typically having a size in the range from 0.01 mm to 5.0 mm, preferably 0.5 mm to 2.5 mm. Preferably, however, the hemostatic composition will be initially prepared from a dry form having a desired particle size (which upon reconstitution, especially by hydration, yields subunits of the requisite size (e.g. hydrogel subunits)) or will be partially or entirely mechanically disrupted to the requisite size prior to a final extrusion or other application step. It is, of course evident, that these mechanical components have to be provided in sterile form (inside and outside) in order to fulfill safety requirements for human use.

[0084] The hemostatic composition according to the present invention is preferably applied in its pasty form to a patient from a container as described in Example 1 with an extrusion force of 40 N or lower, such as lower 30N or lower 20N, preferably in a range of 15 to 30 N.

[0085] Another aspect of the invention concerns a method for providing a ready-to-use hemostatic composition comprising contacting a hemostatic composition according to the present invention.

[0086] The invention is further described in the examples below and the drawing figures, yet without being restricted thereto.

Figure 1 shows the mean extrusion force of glutaraldehyde crosslinked gelatin pastes containing 17.5% (w/w)

crosslinked gelatin with various concentrations of human serum albumin in the thrombin component (extrusion force needed to push product out of syringe at compression speed 250mm/min, calculated at 35 mm distance; all products incubated for 30 minutes at room temperature, quick re-swooshing shortly before extrusion force measurement). The x-axis shows the human serum albumin concentration in the thrombin component in [g/l], the y-axis shows the mean extrusion force in [N].

Figure 2 shows the consistency of crosslinked gelatin pastes containing 17.5% (w/w) crosslinked gelatin depending on the concentration of human serum albumin.

Figure 3 shows the mean extrusion force of genipin crosslinked gelatin pastes containing 17.5% (w/w) gelatin with various concentrations of human serum albumin in the thrombin component. The x-axis shows the human serum albumin concentration in the thrombin component in [g/l], the y-axis shows the mean extrusion force in [N].

Figure 4 shows evaluation of bleeding severity post test article application and approximation.

Figures 5 to 8 show the hemostatic efficacy in Porcine Liver Punch-Biopsy Model of different preparations. The x-axis shows the time after application in [seconds], the y-axis shows percent of hemostatic success (defined as "no bleeding" in Figure 5 and as "no bleeding" or "ooze" in Figure 6).

In Figures 5 and 6 the symbols mean:

- _____ glutaraldehyde crosslinked gelatin with 50 g/l human serum albumin in the thrombin solution (n=8)
- glutaraldehyde crosslinked gelatin with 75 g/l human serum albumin in the thrombin solution (n=8)

In Figures 7 and 8 the symbols mean:

- _____ ≈ 17.5% (w/w) glutaraldehyde crosslinked gelatin
- ≈ 14.5% (w/w) glutaraldehyde crosslinked gelatin
- ≈ 17.5%(w/w) glutaraldehyde crosslinked gelatin plus 2.5% PEG10.000 in thrombin solution

EXAMPLES

Example 1: Determination of Extrusion Force (EF):

[0087] An Instron model 5544 mechanical tester equipped with a 100 N load cell operating at a cross-beam speed of 250 mm/min was used to measure extrusion forces needed to extrude the product from a syringe. The necessary extrusion forces were measured during the complete cross-beam displacement (34mm deflection) which corresponds to a distance a syringe plunger moves in order to extrude almost the entire product out of the syringe. From these forces the mean extrusion forces were calculated as follows:

$$\frac{\text{Total Energy (mJ)}}{\text{Max. Deflection (mm)}} = \text{Mean Force (N)}$$

[0088] Samples for this test were prepared as follows: A 5 ml standard syringe (with a cylindric body having an inner diameter of 12.2mm) with a male luer lock system (the inner nozzle lumen diameter where the adapter is attached measures 2.54mm) is filled with 0.704 g dry mass of the solid sample (approx. 0.8g taking the residual moisture of approx. 12% into account). As a diluent 3.2 ml of a thrombin solution containing 500IU/ml thrombin in 40mM calcium chloride and either 0, 5, 15, 25, 50 or 75 mg/ml human serum albumin was used. The diluent and the solid component were mixed by connecting the syringe holding the diluent (a standard 5ml syringe with a female luer lock system) and the syringe holding the dry component and pushing the contents back and forth at least 10 times (this mixing technique is called "swooshing"). Thereafter the sample was incubated for 30 min at room temperature before measurement. After incubation each sample was "re-swooshed" two times and the syringe holding the product (the syringe that previously held the dry component as mentioned above) was connected to a malleable applicator (female luer connector system, inner tube diameter of 2.29mm holding two wires and having a total length of 141.5mm). The syringe was assembled to the applicator and placed into the Instron set up and the test was started.

The syringes and the applicator were commercially available as parts of the Floseal Hemostatic Matrix product from Baxter.

[0089] The results for a glutaraldehyde crosslinked gelatin as in Floseal are depicted in Fig. 1 and those for a genipin crosslinked gelatin as described below are depicted in Fig. 3 and also shown as corresponding Table 1 and Table 2. The consistency of crosslinked gelatin pastes containing 17.5% (w/w) crosslinked gelatin depending on the concentration of albumin is shown in Fig. 2 (with 0, 25, 50 and 75 g/l human serum albumin provided in the thrombin component).

Table 1:

c(albumin) [g/l] in the thrombin component	extrusion force [N]	std dev
0	40	2,4
5	38	1,5
15	30	2,6
25	25	2,2
50	19	1,5
60	19	1,0

Table 2:

c(albumin) g/l in the thrombin component	extrusion force [N]	std dev
0	54	1.9
15	29	3.6
50	17	2.2

Preparation of genipin crosslinked gelatin:

[0090] Bovine derived collagen was processed via alkaline treatment and subsequently rinsed with deionized process water (DIW) to remove residual salts. Gelatin was extracted by heat treatment and dried in sheets. The sheets were ground to a powder that was to be processed using genipin as a crosslinking agent.

1 kg of gelatin granules were added to 20l of a 10mM genipin solution in DIW. The reaction was performed at neutral pH (7.2) in a jacketed temperature controlled tank at 23°C. Mixing was carried out for 6 hours and the solution was drained off, retaining the solids within a mesh, and rinsed through with DIW to wash out remaining genipin. The material was resuspended in a 5% H₂O₂ solution for 20 hours. The material was rinsed through with DIW to remove the H₂O₂. The solids were pre-dried on filter paper under vacuum and then oven dried for 2.5 days. The dried matrix was ground to a powder and filled into individual plastic syringes before exposure to gamma irradiation.

Example 2: Determination of hemostatic efficiency

Materials and Methods:

Animal Model

[0091] For this model, a midline laparotomy is performed, followed by electrocautery to stop the bleeding from the surgical incision. The liver is exposed and a lobe is isolated. A 10 mm diameter punch biopsy is used to create a series of 2, non-full thickness lesions, approximately 5 mm deep, with the core tissue removed. A pre-treatment assessment is made on the lesion which includes collecting the blood flowing from each lesion for 10 sec. with pre-weighed gauze.

[0092] Test articles are randomized and presented to the surgeon who is blinded to the sample treatment. Approximately 1.0 ml of the assigned test article is topically applied to a lesion. Saline moistened gauze is used to help approximate the test articles to their designated lesions, and the timer is started. The saline moistened approximation gauze is removed after 30 seconds.

[0093] The degree of bleeding is assessed at 30, 60, 90, 120, 300, and 600 sec. after the test articles are applied to their designated lesions as per the depictions in fig. 3 (Bleeding score: 0: no bleeding (product saturated with blood); 1: ooze (blood out of product but no blood drop); 2: very mild (blood drop on the product); 3: mild (blood drop streams down); 4: moderate (small amount of blood streams down); 5: severe (large amount of blood streams down)).

[0094] Product saturated with blood, but without active bleeding is scored as a "0" (zero). Saline is used to irrigate the excess test articles away from the lesions after the 300 sec. assessment. The procedure is repeated and performed in multiple liver lobes. A single surgeon creates, treats, and performs the observation assessments.

Test Article Synthesis

[0095] Test articles for the in vivo evaluation in the porcine-liver model were made by preparing pastes of crosslinked gelatin (in concentrations of 14.5% and 17.5% with 25 or 50 g/l human serum albumin in the thrombin solution (with or without additional 2.5% PEG)).

[0096] The results are depicted in Figs. 5 to 8 showing improved performance with 17.5 % gelatin and less effectiveness in the presence of plasticizers (PEG).

Example 3:

[0097] Gelatin samples were formulated per the package insert for Floseal with a couple key exceptions. First, sodium chloride was used instead of calcium chloride and the gelatin was formulated at 125% solids instead of 100%. The gelatin/thrombin formulations were allowed to stand for 25 minutes and then 1 ml of the preparation was discarded. The other 1 ml of material was applied to the topical hemostasis system (THS). The THS apparatus was previously primed with platelet poor plasma.

The THS is an apparatus designed to simulate a bleeding wound. The artificial wound is a cylindrical hole in a silicone substrate. The surface of the silicone cylinder was coated with a layer of fibrinogen. A syringe pump expelled the clotting fluid (whole blood, plasma, etc.) in this case platelet poor plasma, while the back pressure was recorded. In this experiment the plasma was flowed at a fixed rate of 0.25ml/min through a small hole at the bottom center of the cylindrical wound.

The excess plasma was soaked up with gauze immediately prior to application of the hemostatic matrix. As the plasma continued to flow, 1ml of the hemostatic matrix was applied to the cylindrical wound. This was immediately covered with wet gauze and a fixed pressure was applied. After 30 seconds the weight was removed and the plasma continued to flow for 8-10 minutes, at which point the flow was stopped and the clot set aside in a humidity chamber where it stayed for more than 2 hours. At the end of the two hours, the clot was mounted onto a vibratome at 8°C, where approximately 500 µm thick slabs were sectioned from the clot. These sections were immersed into a PBS buffer. The slabs were stored in a 5°C refrigerator when not in use. The slab was placed onto a coverslip and imaged with a Nikon A1R confocal microscope running the NIS-Elements Advanced Research v3.22.00 Build 710 software. To collect micrographs, a plan fluor 10x objective was used with laser excitation light at 488 nm and an emission collection window from 500-550 nm. A transmitted light image was simultaneously collected using a transmitted light detector. With these imaging parameters, automated stitching performed by the software was used to generate macroscopic maps of samples. Smaller areas of the samples were also characterized by collecting 3D z-stacks of images with an optical slice thickness of 5.125 µm. The composite confocal map was used to identify the gelatin granules that are located at the surface, and which were sectioned. This was important for positioning of the elasticity measurement in the atomic force microscope (AFM). The clot slab was mounted in a Veeco Multimode AFM. The multimode was equipped with a Nanoscope V controller and a JV piezoelectric scanner. The force measurements were made with a Novascan AFM cantilever which supported a 4.5 µm polystyrene sphere. The cantilever's force constant was determined to be 0.779 N/m by the thermal tune method. The cantilever was positioned above the center of the gelatin granule, and then a 16x16 array of force measurements were made. Each force curve involved moving the gelatin granule up into contact with the polystyrene sphere, and continuing to move the granule up until the cantilever deflection reached a preset trigger value of 2 volts, at which point the gelatin was retracted a distance of 1.00 micron from the trigger location.

Discussion

[0098] The fluorescence data shows that the glutaraldehyde crosslinked gelatin is not uniformly crosslinked. Instead, the crosslinking density seems higher around the edges of the granules, with the central portion of the granule being significantly less crosslinked than the edges. In contrast, the genipin crosslinked gelatin appears uniformly (homogeneously) crosslinked throughout the granules. There are no substantial edge effects to the fluorescence intensity. The fluorescence intensity of the genipin and glutaraldehyde crosslinked materials cannot be directly compared, because of the potential fluorescence differences attributed to the crosslinkers themselves. However, the AFM measured elastic modulus measurement show that the genipin crosslinked gelatin is stiffer than the glutaraldehyde crosslinked gelatin, which appears to be softer (more flexible).

Claims

1. 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

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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. Hemostatic composition according to claim 1, wherein the extrusion enhancer is albumin in an amount of between 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. Hemostatic composition according to claim 1 to 2, wherein the crosslinked gelatin is glutaraldehyde-crosslinked gelatin or genipin-crosslinked gelatin.
4. Hemostatic composition according to any one of claims 1 to 3, wherein the crosslinked gelatin is type B gelatin.
5. Hemostatic composition according to any one of claims 1 to 4, wherein the crosslinked gelatin is present as granular material.
6. 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. 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. Hemostatic composition to any one of claims 1 to 7 for use in the treatment of an injury selected from the group consisting of a wound, a hemorrhage, damaged tissue, bleeding tissue and/or bone defects.
9. 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. Kit according to claim 9, wherein the pharmaceutically acceptable diluent comprises a buffer or buffer system, preferably at a pH of 3.0 to 10.0.
11. Kit according to claim 9 or 10, wherein the pharmaceutically acceptable diluent comprises thrombin, preferably 10 to 1000 I.U. thrombin/ml, especially 250 to 700 I.U. thrombin/ml.
12. Kit according to any one of claims 9 to 11, wherein the pharmaceutically acceptable diluent contains a substance selected from the group consisting of NaCl, CaCl₂ and sodium acetate.
13. 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. Method according to claim 13 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.

Patentansprüche

1. Hämostatische Zusammensetzung, umfassend zur Verwendung bei Hämostase geeignete vernetzte Gelatine in

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partikulärer Form, wobei die Zusammensetzung in einer Pastenform vorliegt, die 15,0 bis 19,5% (w/w) vernetzte Gelatine, vorzugsweise 16,0 bis 19,5% (w/w), 16,5 bis 19,5% (w/w), 17,0 bis 18,5% (w/w) oder 17,5 bis 18,5% (w/w), mehr bevorzugt 16,5 bis 19,0% (w/w) oder 16,8 bis 17,8% (w/w), besonders bevorzugt 16,5 bis 17,5% (w/w), enthält und wobei die Zusammensetzung einen Extrusionsförderer umfasst, welcher Extrusionsförderer Albumin in einer Menge von zwischen 0,5 und 5,0% (w/w) ist.

2. Hämostatische Zusammensetzung gemäß Anspruch 1, wobei der Extrusionsförderer Albumin in einer Menge von zwischen 1,0 und 5,0% (w/w), vorzugsweise 2,0 und 4,5% (w/w), mehr bevorzugt 1,5 und 5,0% (w/w), besonders bevorzugt etwa 1,5% (w/w) ist.

3. Hämostatische Zusammensetzung gemäß Anspruch 1 bis 2, wobei die vernetzte Gelatine mit Glutaraldehyd vernetzte Gelatine oder mit Genipin vernetzte Gelatine ist.

4. Hämostatische Zusammensetzung gemäß einem der Ansprüche 1 bis 3, wobei die vernetzte Gelatine Typ B-Gelatine ist.

5. Hämostatische Zusammensetzung gemäß einem der Ansprüche 1 bis 4, wobei die vernetzte Gelatine als granuläres Material vorliegt.

6. Hämostatische Zusammensetzung gemäß einem der Ansprüche 1 bis 5, wobei die vernetzte Gelatine eine Partikelgröße von 100 bis 1000 μm , vorzugsweise von 200 bis 800 μm , am meisten bevorzugt von 350 bis 550 μm , aufweist.

7. Hämostatische Zusammensetzung gemäß einem der Ansprüche 1 bis 6, wobei die Zusammensetzung Thrombin, vorzugsweise 10 bis 1000 I.U. Thrombin/ml, insbesondere 250 bis 700 I.U. Thrombin/ml, aufweist.

8. Hämostatische Zusammensetzung gemäß einem der Ansprüche 1 bis 7, zur Verwendung bei der Behandlung einer Verletzung, die ausgewählt ist aus der Gruppe, bestehend aus einer Wunde, einer Blutung, geschädigtem Gewebe, blutendem Gewebe und/oder Knochendefekten.

9. Kit zur Herstellung einer fließfähigen Paste aus vernetzter Gelatine für die Behandlung einer Verletzung, die ausgewählt ist aus der Gruppe, bestehend aus einer Wunde, einer Blutung, geschädigtem Gewebe und/oder blutendem Gewebe, umfassend

a) eine trockene hämostatische Zusammensetzung, umfassend vernetzte Gelatine in partikulärer Form, die zu einer fließfähigen Paste rekonstituiert werden muss, enthaltend 15,0 bis 19,5% (w/w) vernetzte Gelatine, vorzugsweise 16,0 bis 19,5% (w/w), 16,5 bis 19,5% (w/w), 17,0 bis 18,5% (w/w) oder 17,5 bis 18,5% (w/w), mehr bevorzugt 16,5 bis 19,0% (w/w) oder 16,8 bis 17,8% (w/w), besonders bevorzugt 16,5 bis 17,5% (w/w), und

b) ein pharmazeutisch akzeptables Verdünnungsmittel zur Rekonstitution der hämostatischen Zusammensetzung, wobei entweder die Zusammensetzung oder das Verdünnungsmittel Albumin in einer Menge umfasst, die zu einer Albuminkonzentration in der rekonstituierten Paste von zwischen 0,5 und 5,0% (w/w), vorzugsweise 1,0 und 5,0% (w/w), bevorzugt 2,0 und 4,5% (w/w), mehr bevorzugt 1,5 und 5,0% (w/w), besonders bevorzugt etwa 1,5% (w/w), führt.

10. Kit gemäß Anspruch 9, wobei das pharmazeutisch akzeptable Verdünnungsmittel einen Puffer oder ein Puffersystem, vorzugsweise bei einem pH von 3,0 bis 10,0, umfasst.

11. Kit gemäß Anspruch 9 oder 10, wobei das pharmazeutisch akzeptable Verdünnungsmittel Thrombin, vorzugsweise 10 bis 1000 I.U. Thrombin/ml, insbesondere 250 bis 700 I.U. Thrombin/ml, umfasst.

12. Kit gemäß einem der Ansprüche 9 bis 11, wobei das pharmazeutisch akzeptable Verdünnungsmittel eine Substanz enthält, die ausgewählt ist aus der Gruppe, bestehend aus NaCl, CaCl_2 und Natriumacetat.

13. Verfahren zur Bereitstellung einer gebrauchsfertigen Form einer hämostatischen Zusammensetzung gemäß einem der Ansprüche 1 bis 7, wobei die hämostatische Zusammensetzung in einer ersten Spritze bereitgestellt wird und ein Verdünnungsmittel zur Rekonstitution in einer zweiten Spritze bereitgestellt wird, die erste und die zweite Spritze miteinander in Kontakt gebracht werden und die Flüssigkeit in die erste Spritze eingebracht wird, um eine fließfähige Form der hämostatischen Zusammensetzung zu erzeugen; und optional Rückbefördern der fließfähigen Form der

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hämostatischen Zusammensetzung in die zweite Spritze wenigstens für ein Mal.

14. Verfahren gemäß Anspruch 13, wobei die fließfähige Form der hämostatischen Zusammensetzung Partikel enthält, die zu mehr als 50% (w/w) eine Größe von 100 bis 1000 μm , vorzugsweise zu mehr als 80% (w/w) eine Größe von 100 bis 1000 μm , aufweisen.

Revendications

1. Composition hémostatique comprenant de la gélatine réticulée sous forme de particules appropriées pour une utilisation en hémostase, la composition étant présente sous forme de pâte contenant de 15,0 à 19,5 % (p/p) de gélatine réticulée, de préférence de 16,0 à 19,5 % (p/p), de 16,5 à 19,5 % (p/p), de 17,0 à 18,5 % (p/p) ou de 17,5 à 18,5 % (p/p), de préférence encore de 16,5 à 19,0 % (p/p) ou de 16,8 à 17,8 % (p/p), de manière particulièrement préférée de 16,5 à 17,5 % (p/p), et la composition comprenant un agent d'amélioration de l'extrusion, l'agent d'amélioration de l'extrusion étant l'albumine en une quantité comprise entre 0,5 et 5,0 % (p/p).
2. Composition hémostatique selon la revendication 1, dans laquelle l'agent d'amélioration de l'extrusion est l'albumine en une quantité comprise entre 1,0 et 5,0 % (p/p), de préférence entre 2,0 et 4,5 % (p/p), de préférence encore de 1,5 à 5,0 % (p/p), de manière particulièrement préférée environ 1,5 % (p/p).
3. Composition hémostatique selon la revendication 1 ou 2, dans laquelle la gélatine réticulée est de la gélatine réticulée de glutaraldéhyde ou de la gélatine réticulée de génipine.
4. Composition hémostatique selon l'une quelconque des revendications 1 à 3, dans laquelle la gélatine réticulée est de la gélatine de type B.
5. Composition hémostatique selon l'une quelconque des revendications 1 à 4, dans laquelle la gélatine réticulée est présente sous forme d'un matériau granulaire.
6. Composition hémostatique selon l'une quelconque des revendications 1 à 5, dans laquelle la gélatine réticulée dont les particules ont une taille de 100 à 1 000 μm , de préférence de 200 à 800 μm , de manière préférée entre toutes de 350 à 550 μm .
7. Composition hémostatique selon l'une quelconque des revendications 1 à 6, dans laquelle la composition contient de la thrombine, de préférence de 10 à 1 000 U.I. de thrombine/mL, en particulier de 250 à 700 U.I. de thrombine/mL.
8. Composition hémostatique selon l'une quelconque des revendications 1 à 7, destinée à être utilisée dans le traitement d'une blessure choisie dans le groupe constitué par une plaie, une hémorragie, un tissu endommagé, un saignement du tissu et/ou des défauts osseux.
9. Kit de préparation d'une pâte fluide de gélatine réticulée destinée au traitement d'une blessure choisie dans le groupe constitué par une plaie, une hémorragie, un tissu endommagé et/ou un saignement du tissu comprenant :
 - a) une composition hémostatique sèche comprenant de la gélatine réticulée sous forme de particules pouvant être reconstituée en une pâte fluide contenant de 15,0 à 19,5 % (p/p) de gélatine réticulée, de préférence de 16,0 à 19,5 % (p/p), de 16,5 à 19,5 % (p/p), de 17,0 à 18,5 % (p/p) ou de 17,5 à 18,5 % (p/p), de préférence encore de 16,5 à 19,0 % (p/p) ou de 16,8 à 17,8 % (p/p), de manière particulièrement préférée de 16,5 à 17,5 % (p/p), et
 - b) un diluant pharmaceutiquement acceptable destiné à reconstituer la composition hémostatique, soit la composition, soit le diluant comprenant de l'albumine en une quantité conduisant à une concentration en albumine dans la pâte reconstituée comprise entre 0,5 et 5,0 % (p/p), de préférence entre 1,0 et 5,0 % (p/p), de préférence entre 2,0 et 4,5 % (p/p), de préférence encore de 1,5 à 5,0 % (p/p), de manière particulièrement préférée environ 1,5 % (p/p).
10. Kit selon la revendication 9, dans laquelle le diluant pharmaceutiquement acceptable comprend un tampon ou un système de tampons, de préférence à un pH de 3,0 à 10,0.
11. Kit selon la revendication 9 ou 10, dans lequel le diluant pharmaceutiquement acceptable comprend de la thrombine,

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de préférence de 10 à 1 000 U.I. de thrombine/mL, en particulier de 250 à 700 U.I. de thrombine/mL.

12. Kit selon l'une quelconque des revendications 9 à 11, dans lequel le diluant pharmaceutiquement acceptable contient une substance choisie dans le groupe constitué par NaCl, CaCl₂ et l'acétate de sodium.

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13. Procédé de mise à disposition d'une forme de composition hémostatique prête à l'emploi selon l'une quelconque des revendications 1 à 7, dans lequel la composition hémostatique est fournie dans une première seringue et un diluant destiné à la reconstitution est fourni dans une seconde seringue, les première et seconde seringues sont reliées l'une à l'autre, et le liquide est amené à l'intérieur de la première seringue afin de produire la composition hémostatique sous une forme fluide ; et éventuellement ramener au moins une fois la composition hémostatique sous forme fluide à la seconde seringue.

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14. Procédé selon la revendication 13 dans lequel la composition hémostatique sous forme fluide contient des particules dont plus de 50 % (p/p) sont d'une taille de 100 à 1 000 μm , de préférence plus de 80 % (p/p) sont d'une taille de 100 à 1 000 μm .

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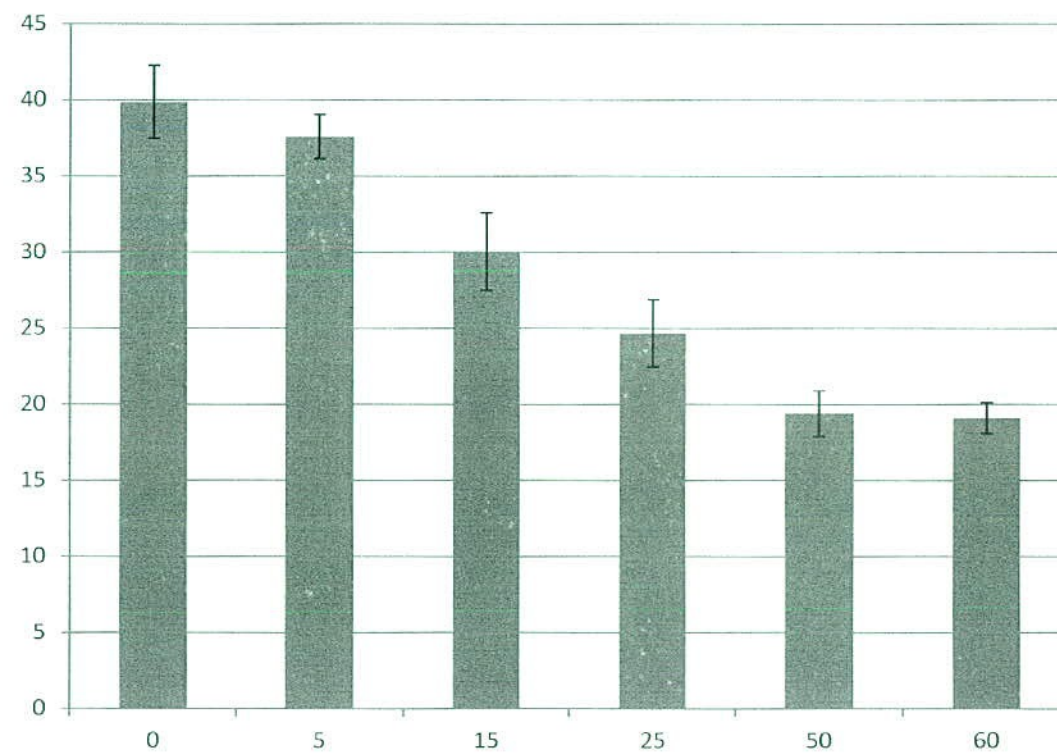


Fig. 1

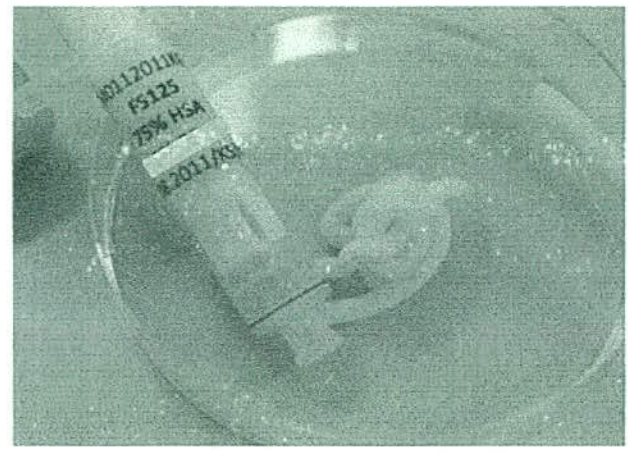
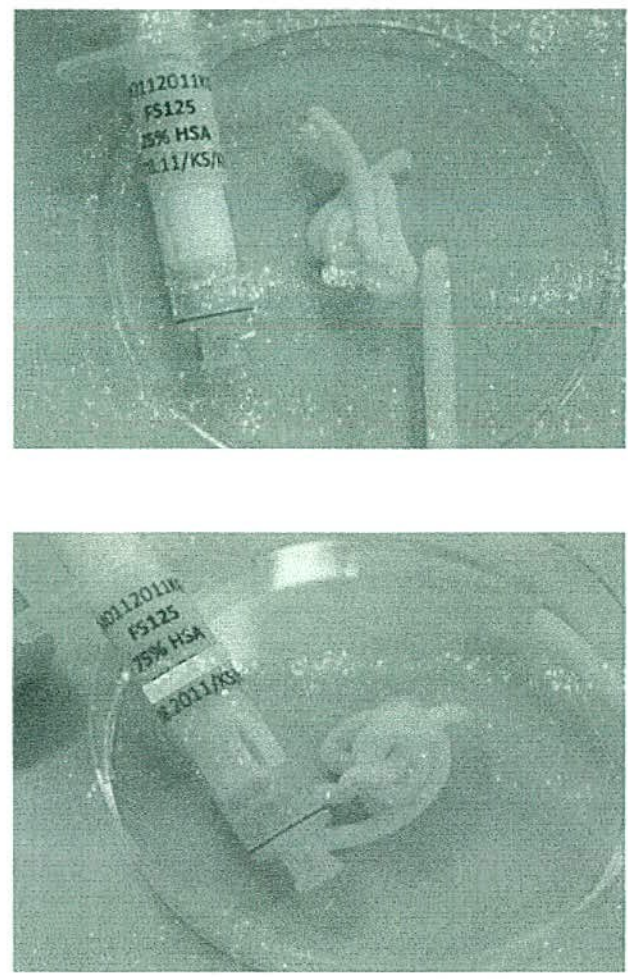


Fig. 2

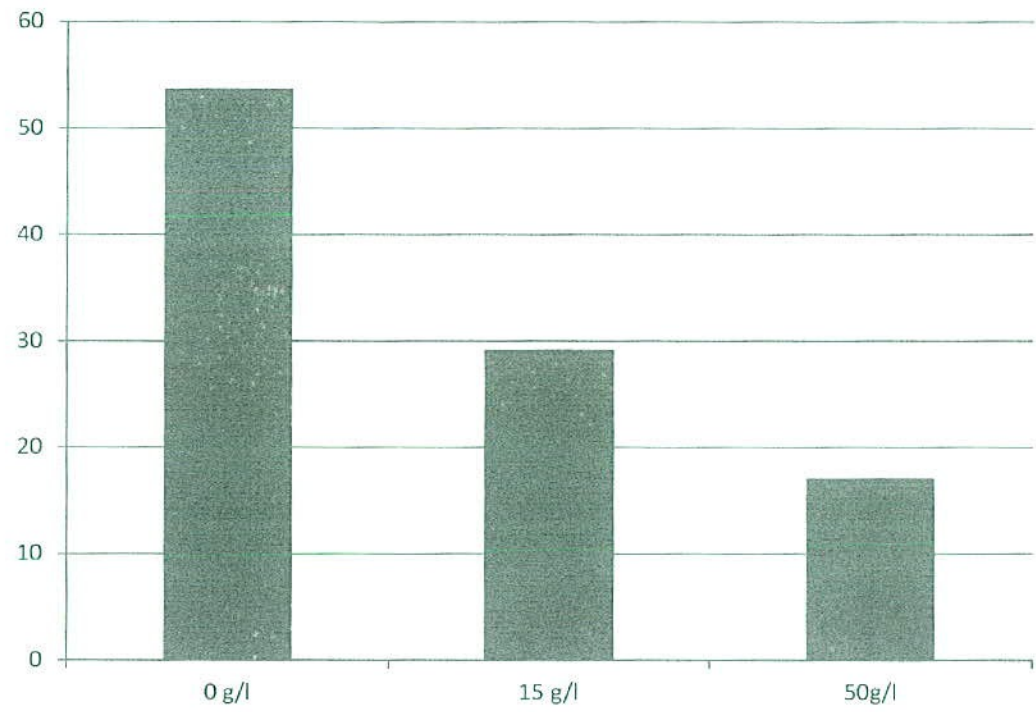
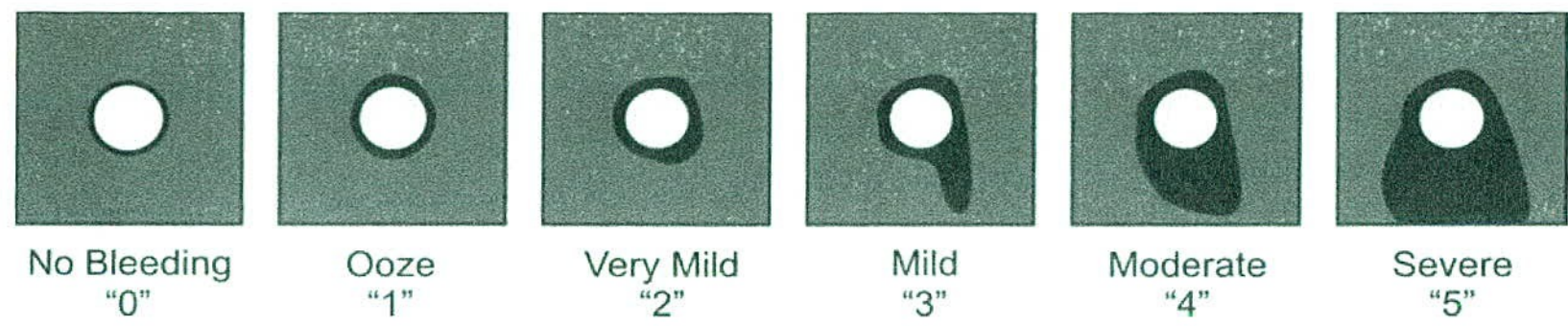


Fig 3



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Fig. 4

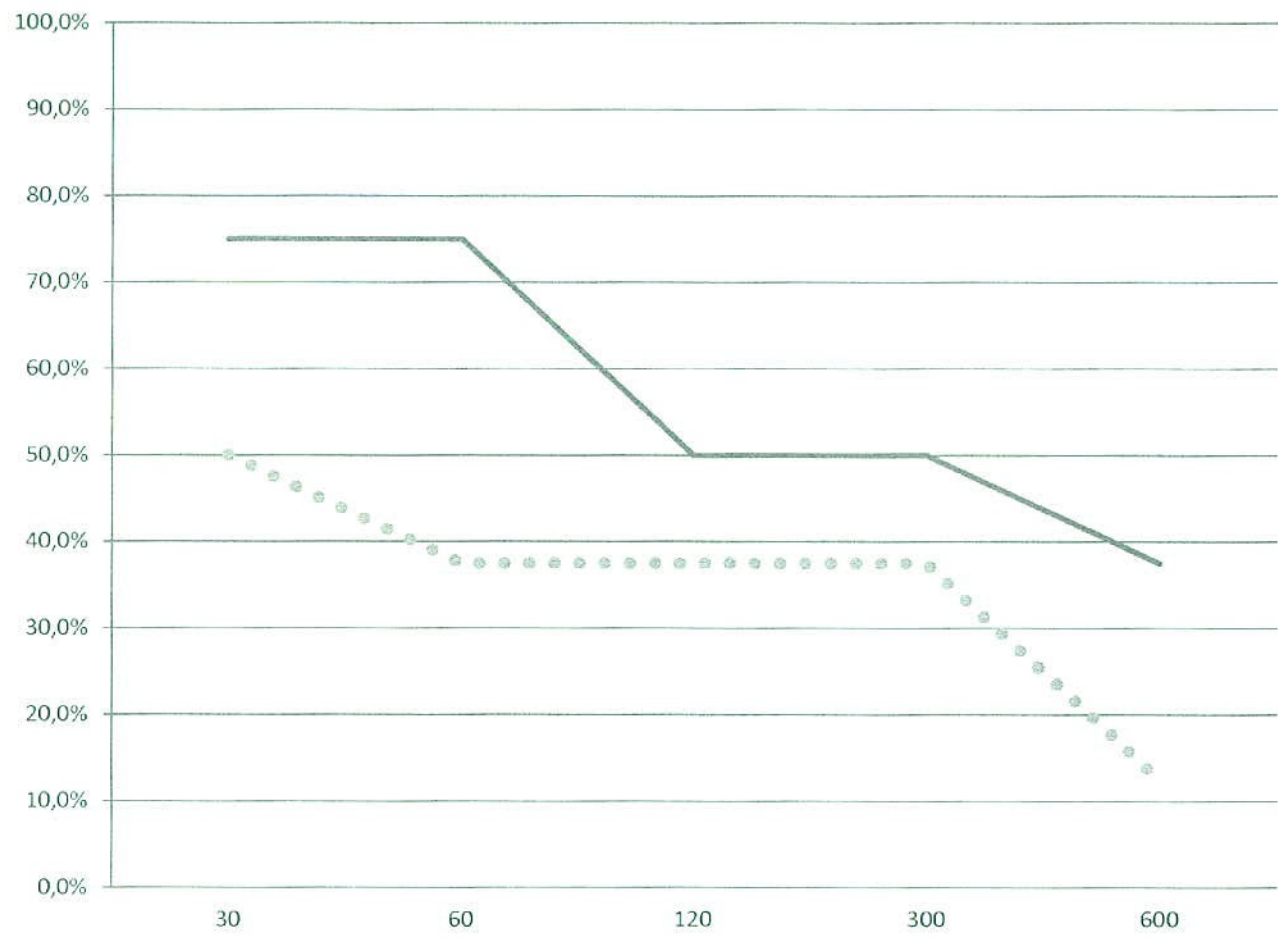


Fig. 5

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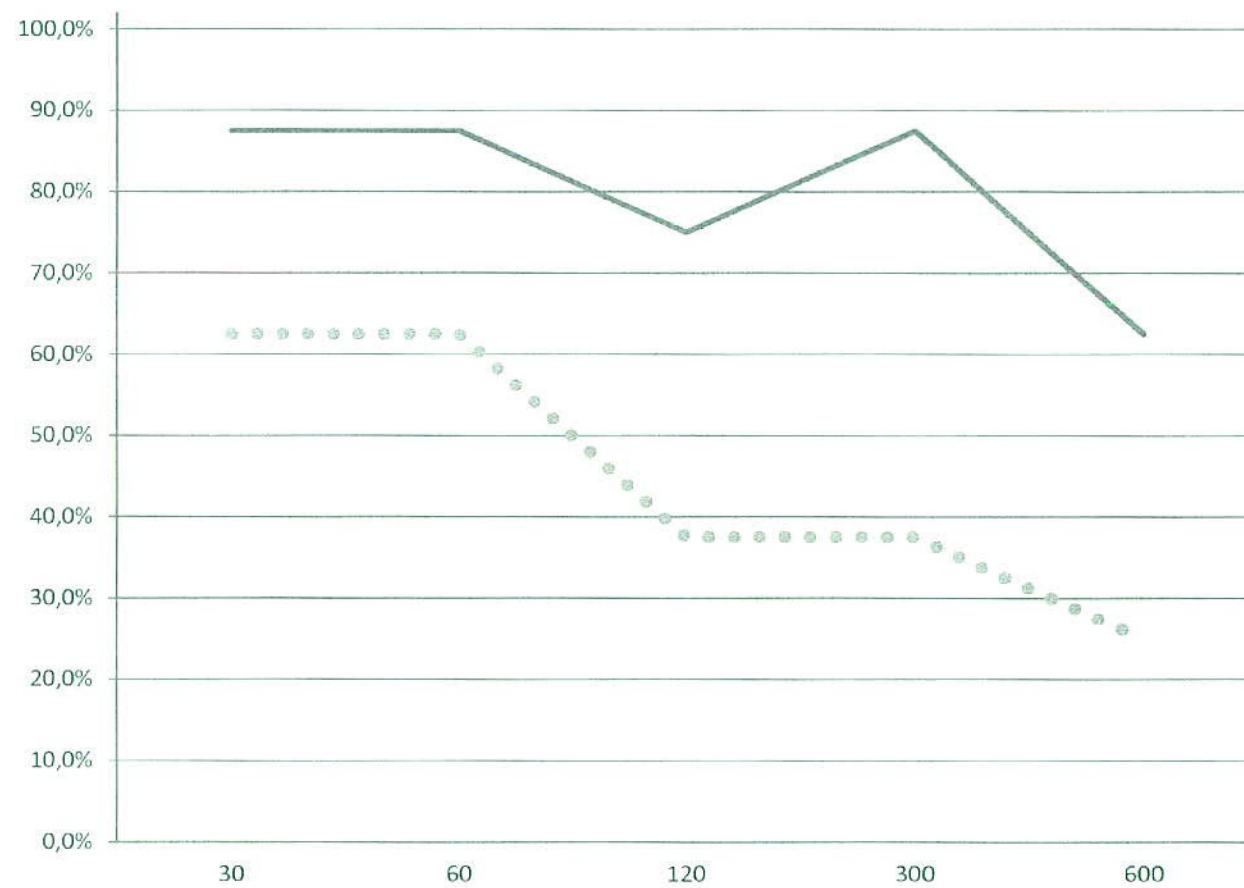


Fig. 6

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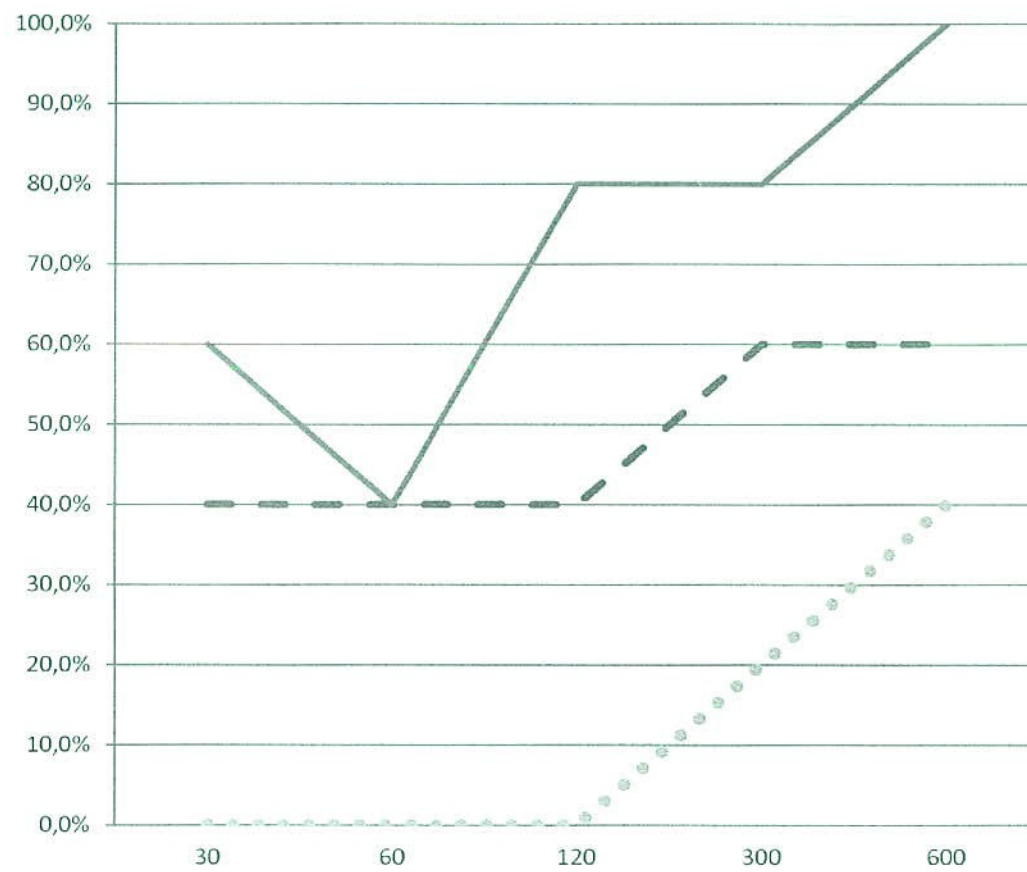


Fig. 7

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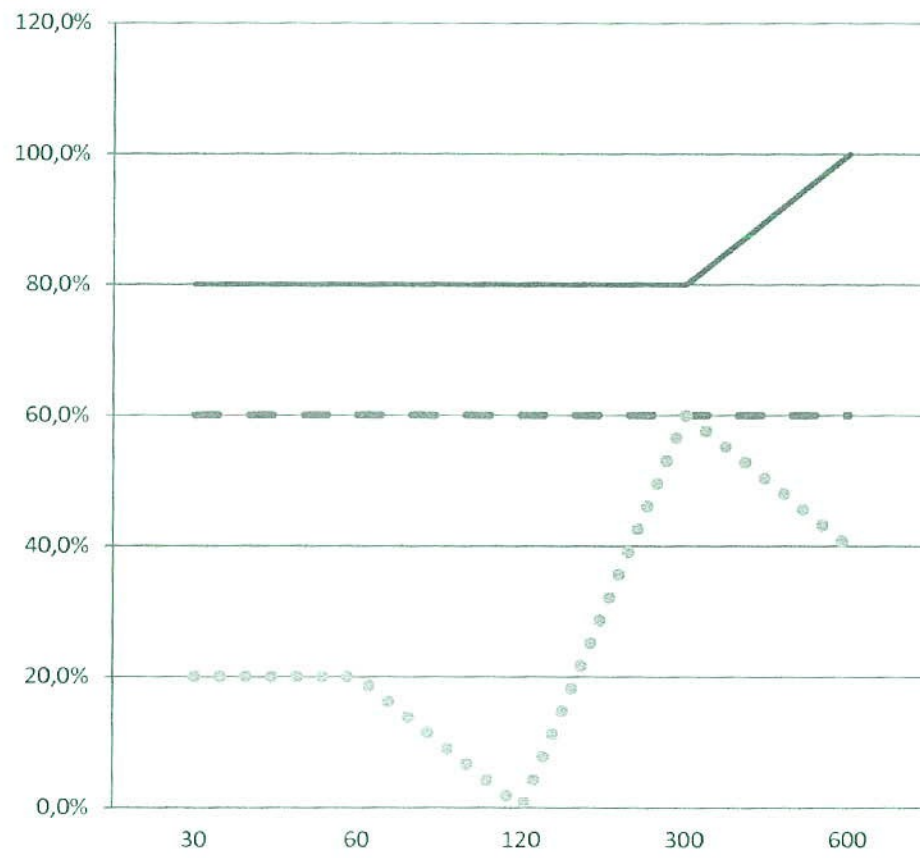


Fig. 8

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REFERENCES CITED IN THE DESCRIPTION

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