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Datasheet for the decision of 21 September 2023

Case Number: T 3054/19 - 3.3.10

Application Number: 14729220.5

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Language of the proceedings: EN

Title of invention:
METHOD FOR CROSSLINKING HYALURONIC ACID; METHOD FOR PREPARING AN INJECTABLE HYDROGEL; HYDROGEL OBTAINED; USE OF THE OBTAINED HYDROGEL

Patent Proprietor:
Anteis SA

Opponent:
Laboratoires Vivacy

Headword:
METHOD FOR PREPARING AN INJECTABLE HYDROGEL/Anteis

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(1)

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 3054/19 - 3.3.10

D E C I S I O N
of Technical Board of Appeal 3.3.10
of 21 September 2023

Appellant: (Opponent)	Laboratoires Vivacy 44 rue Paul Valéry 75116 Paris (FR)
Representative:	Tripoz, Inès Cabinet Tripoz Le Pôle Sud 22 rue Seguin 69002 Lyon (FR)
Respondent: (Patent Proprietor)	Anteis SA 18 Chemin des Aulx 1228 Plan-Les-Ouates (CH)
Representative:	Ricker, Mathias Wallinger Ricker Schlotter Tostmann Patent- und Rechtsanwälte Partnerschaft mbB Zweibrückenstraße 5-7 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 November 2019 rejecting the opposition filed against European patent No. 3007737 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	P. Gryczka
Members:	J.-C. Schmid
	F. Blumer

Summary of Facts and Submissions

I. The appellant (opponent) lodged an appeal against the decision of the opposition division rejecting the opposition against European patent No. 3 007 737, claim 1 thereof reading as follows:

"1. A method for crosslinking hyaluronic acid, or one of its salts, and optionally other biocompatible polymers, characterized in that it comprises at least the steps of:

a) preparing a first aqueous phase of hyaluronic acid, and optionally of other biocompatible polymers, partly crosslinked, characterized by:
- the addition of hyaluronic acid or one of its salts and optionally of other biocompatible polymers, in an aqueous solution in order to obtain a hyaluronic acid concentration C1
- the addition of an amount Q1 of crosslinking agent
- achieving partial crosslinking of the hyaluronic acid by controlling the temperature T1 and the duration t1 of the crosslinking reaction,

wherein the prepared first aqueous phase of partially crosslinked hyaluronic acid is not converted into particles;

b) preparing at least one second aqueous phase of hyaluronic acid and optionally of other biocompatible polymers, partly crosslinked, characterized by:
- the addition of hyaluronic acid, or one of its salts and optionally of other biocompatible polymers, in an

aqueous solution in order to obtain a hyaluronic acid concentration C2

- the addition of an amount Q2 of crosslinking agent

- achieving partial crosslinking of the hyaluronic acid by controlling the temperature T2 and the duration t2 of the crosslinking reaction,

wherein the prepared at least one second aqueous phase of partially crosslinked hyaluronic acid is not converted into particles;

c) adding the at least one second partly crosslinked hyaluronic acid phase into the first phase, and then producing a mixture of said at least two phases by optionally adding an additional amount Qm of crosslinking agent; and

d) continuing the crosslinking of the mixture made beforehand by controlling the temperature Tm and the duration tm of the crosslinking reaction,

wherein the crosslinking method does not involve the addition of crosslinked hyaluronic acid particles or one of its salts, or of any other polymer, during steps a, b, c and d of said crosslinking method."

II. The appellant had filed an opposition requesting revocation of the patent-in-suit in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC), insufficient disclosure of the invention (Article 100(b) EPC) and extension of the subject-matter of the patent-in-suit beyond the content of the application as filed (Article 100(c) EPC).

Inter alia the following documents were submitted in the opposition proceedings:

(2) EP-A-2 011 816 and
(3) WO-A-2009/071697.

III. According to the opposition division, the grounds for opposition pursuant Article 100(b),(c) EPC did not prejudice the maintenance of the patent in suit and the subject-matter of claim 11 was novel over the cited documents.

With respect to inventive step, document (3) represented the closest prior art to the invention. The problem to be solved was the provision of an alternative injectable hydrogel based on hyaluronic acid, which was stabilized by crosslinking, but still had viscosity properties enabling it to be satisfactorily ejected through an needle causing minimum discomfort to the patient. The proposed solution, i.e. the manufacturing process including steps c) and d) of claim 1 of the patent as granted was not obvious in the light of document (3) alone.

IV. The appellant contested the conclusions of the opposition division with respect to all issues. In particular the appellant submitted that the subject-matter of claim 1 did not involve an inventive step starting from document (3) as the closest prior art to the invention in combination with document (2).

V. With the response to the statement of the grounds of appeal dated 6 July 2000, the patent proprietor (respondent) filed auxiliary requests 1 and 2.

Claim 1 of auxiliary request 1 differs from claim 1 of the patent as granted in that the crosslinking temperature T2 is greater than or equal to the temperature T1, and the crosslinking temperature Tm is greater than the temperature T2.

Claim 1 of auxiliary request 2 differs from claim 1 of the patent as granted in that T1 and T2 are less than 35°C and Tm is greater than 45°C.

VI. With the letter dated 25 July 2023, the respondent furthermore filed auxiliary requests 3 to 5, which differ from the patent as granted (main request) and auxiliary requests 1 and 2, respectively, by the deletion of claims 11 to 16.

VII. During the oral proceedings before the Board held on 21 September 2023, the respondent further filed auxiliary request 6.

Claim 1 of auxiliary request 6 differs from claim 1 of the patent as granted in that the second aqueous partly crosslinked hyaluronic acid phase has a partial degree of crosslinking greater than that of the first aqueous partly crosslinked hyaluronic acid phase.

VIII. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed (main request), or subsidiarily, that the patent be maintained on the basis of one of auxiliary requests 1 or 2 filed with the response to the statement of the grounds of appeal dated 6 July 2020, auxiliary requests 3 to 5 filed with the letter

dated 25 July 2023 or auxiliary request 6 filed on 21 September 2023 during the oral proceedings.

IX. At the end of the oral proceedings before the board, the decision of the Board was announced.

Reasons for the Decision

Inventive step

Main request (patent as granted)

1. Closest prior art

It is not contested that document (3) may represent the closest prior art to the invention. This document relates to the field of crosslinked biodegradable hydrogels having aesthetical or medicinal applications (page 1, lines 1-2). The hydrogels described in document (3) possess good properties in terms of persistence in vivo and viscosity in order to guarantee good injectability when using fine needles (page 1, lines 14 to 18).

Document (3) discloses a process for preparing a cohesive hydrogel comprising
- preparing a first aqueous phase of hyaluronic acid and adding BDDE to achieve partial crosslinking of the hyaluronic acid,
- preparing a second aqueous phase of hyaluronic acid and adding BDDE to achieve partial crosslinking of the hyaluronic acid, and
- mixing the two partly crosslinked hyaluronic acids (see examples 1 to 3; claim 16).

The hyaluronic gels prepared in examples 2 and 3 have a good balance between injectability and remanence (see example 4; page 4, line 25 to page 6, line 9).

The process of claim 1 of the patent as granted differs from the process disclosed in document (3) only in that the crosslinking of the mixture obtained after mixing the two partly crosslinked hyaluronic acids is continued by optionally adding an additional amount of crosslinking agent and by controlling the temperature Tm and the duration tm of the crosslinking reaction.

2. *Technical problem*

The respondent defined the technical problem to be solved as the provision of an alternative process for preparing an injectable hyaluronic acid gel having a good balance of injectability and remanence.

3. *Solution*

The proposed solution is the process of claim 1 of the patent as granted characterised by step (d) of continuing the crosslinking of the obtained mixture by controlling the temperature Tm and the duration tm of the crosslinking reaction, optionally by adding an additional amount of crosslinking agent (part of step (c)).

4. Obviousness

It remains to be decided whether, in view of the cited prior art, the proposed solution of further cross-linking the mixture of the two partially cross-linked hyaluronic acids obtained by the process of document (3) is obvious to the person skilled in the art in

order to provide an alternative process for the production of a hyaluronic acid gel.

4.1 Document (2) also relates to injectable gels of co-cross-linked polysaccharides which are used in reconstructive surgery, cosmetic surgery and surgery for filling biological tissues.

The gel disclosed in document (2) is a co-crosslinked gel which is a mixture of a first gel of hyaluronic acid partly crosslinked (rate of 0.21 to 0.9) in the form of particles evenly distributed in a second gel of weakly crosslinked hyaluronic acid (rate of 0.03 to 0.3), where the first gel is bound covalently with second gel (claims 1 to 5; paragraph [0048]).

The person skilled in the art wishing to provide an alternative process to that of document (3) would logically have turned document (2) in view of the similarity of chemical structure of the gels, especially as documents (2) and (3) both deal with injectable gels for use in reconstructive or cosmetic surgery.

The skilled person would thus find in document (2) the solution of further cross-linking the mixture of the two partially cross-linked hyaluronic acids obtained in document (3) in order to provide a cohesive gel where the first gel is bound covalently with second gel.

4.2 According to the respondent, document (3) dissuades the skilled person from creating covalent bonds between the two partially cross-linked hyaluronic acids, because the mixture of pre-crosslinked hyaluronic acids without creation of a covalent bond between them is the key feature of the invention of document (3), which teaches

that the mixed hyaluronic acids become indissociable from one another, thus generating a network of intertwined crosslinked gels, the cohesiveness of which is similar to that of interpenetrating polymer networks exhibiting their advantages without their disadvantages.

The Board agrees with the respondent that there is no incentive in document (3) to continue cross-linking after the two partially cross-linked hyaluronic acids have been mixed and that advantages of not carrying out the crosslinking of the mixture are also indicated in document (3), e.g. the ability to adjust the rheological properties of the mixture.
Furthermore, the person skilled in the art is aware that the properties specifically linked to mixture of two partially cross-linked hyaluronic acids would longer not be present if co-crosslinking is carried out.

However, retaining these properties specific to the mixture is not part of the technical problem. Indeed, the technical problem is the provision of an alternative process for preparing an injectable hyaluronic acid gel having a good balance of injectability and remanence. Document (2) discloses that a co-crosslinked hyaluronic acids gel has a good balance of injectability and remanence (see paragraph [0026]).

Document (3) does not contain any information to the effect that further cross-linking of the mixture of the two cross-linked hyaluronic acids would be detrimental to obtaining an injectable hyaluronic gel. The lack of suggestion to continue cross-linking after mixing the two cross-linked hyaluronic acids in document (3) is

not equivalent to a dissuasive instruction not to follow the teaching in document (2) to continue cross-linking to obtain a co-crosslinked hyaluronic acids gel having a good balance of injectability and remanence.

The Respondent's argument based on the dissuasive teaching in document (3) must therefore be rejected.

4.3 According to the respondent, the skilled man would not have turned to document (2) when looking for an alternative process, since this document relates to gels comprising particles of reticulated hyaluronic acid, which are excluded by the claimed process.

The gel particles described in document (2) are hyaluronic acid gel fragments. The term particle is used because the partially cross-linked hyaluronic acids with higher degree of crosslinking can be milled and dispersed in the weakly crosslinked hyaluronic acid (see paragraph [0039]). However, these particles are not rigid and remain soft (paragraph [0043]). The gel particles disclosed in documents (2) and the first gel disclosed in document (3) are formed from partially cross-linked hyaluronic acids. The person skilled in the art would therefore have been prompted to turn to document (2) in order to provide an alternative process and, as a result, would have learned from document (2) that covalent bonds can be formed between the highly crosslinked hyaluronic acid and the weakly crosslinked hyaluronic acid.

4.4 The Board therefore comes to the conclusion that the subject-matter of claim 1 of the main request is obvious over the combination of document (3) with document (2).

Auxiliary requests 1 and 2

5. In claim 1 of auxiliary request 1, the crosslinking temperature T2 is greater than or equal to the temperature T1, and the crosslinking temperature of the mixture Tm is greater than the temperature T2.
In claim 1 of auxiliary request 2, T1 and T2 are less than 35°C and Tm is greater than 45°C.

Document (3) teaches that the cross-linking reactions are reactions that are well known and the person skilled in the art will be able to develop and optimise the cross-linking conditions, such as cross-linking rate, temperature, pH … (page 9, lines 23 to 29).

In the working examples of document (3), the first and the second crosslinking reactions are carried out at 50°C during 2H20 (see page 13, lines 19 to 23; page 14, lines 10 to 15).

The respondent argued that this limitation to certain temperature ranges was intended to further distinguish the claimed process from the process of document (3). However, the respondent admitted that in the absence of further characteristics, such as the reaction duration or the amount of the crosslinking agent, the temperature characteristic present in auxiliary request 1 and 2 is not directly linked to any effect on the structure of the gel obtained by the claimed process.

In the absence of any surprising technical effect, the temperature parameters introduced in claim 1 of auxiliary requests 1 or 2 are therefore obvious to those skilled in the art.

Consequently, the subject-matter of claim 1 of auxiliary request 1 and 2 lacks also an inventive step.

Auxiliary request 3 to 5

6. Claim 1 of auxiliary requests 3 to 5 is identical to claim 1 of the main and auxiliary requests 1 and 2, respectively.

Therefore, these requests are rejected for the same reason as the main and auxiliary requests 1 and 2.

Auxiliary request 6

7. This auxiliary request was filed at a very late stage of the appeal procedure namely during the oral proceedings before the board. According to the respondent, the filing of this auxiliary request was a response to the finding during the oral proceedings that the temperature characteristic alone had no impact on the structural characteristics of the gel formed.

However, the structural feature relating to the gel prepared by the claimed process introduced in claim 1 of auxiliary request 6, namely that the second aqueous phase of partially cross-linked hyaluronic acid has a higher partial degree of cross-linking than the first aqueous phase of partially cross-linked hyaluronic acid, is already known from document (3) (see claim 2; example 1).

The amendment carried out in claim 1 of auxiliary request 6, *prima facie*, does not overcome the objection of inventive step raised by the appellant. Therefore, already for this reason, late-filed auxiliary request 6

is not admitted in the appeal proceedings (Article 13(1) RPBA).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

C. Rodríguez Rodríguez P. Gryczka

Decision electronically authenticated