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D E C I S I O N
of 29 November 1996

Case Number: T 0137/93 - 3.3.4

Application Number: 87905702.4

Publication Number: 0318512

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Language of the proceedings: EN

Title of invention:
Delivery systems for pharmacological agents

Applicant:
Emisphere Technologies, Inc.

Opponent:
-

Headword:
DELIVERY SYSTEMS FOR PHARMACOLOGICAL AGENTS/Emisphere Technologies

Relevant legal provisions:
EPC Art. 54, 56, 84, 123(2)

Keyword:
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

Case Number: T 0137/93 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 29 November 1996

Appellant: Emisphere Technologies, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 13 August 1992 refusing European patent application No. 87 905 702.4 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: D. D. Harkness
J.-C. Saisset

Summary of Facts and Submissions

I. European patent application No. 87 905 702.4 filed under the PCT and relating to a delivery system for pharmacological agents was refused by the Examining Division.

The decision was taken on the basis of claims 1 to 13 filed on 18 February 1992 of which claims 1, 10 and 13 read as follows:

"1. Composition comprising a pharmacologically active agent encapsulated within protenoid microspheres having diameters less than 10 µm and formed from thermal condensation polymers of mixed amino acids wherein said proteinoid micropheres release said pharmacological agent within a selected pH range.

10. Method for microencapsulating a pharmacologically active agent for targeted release within a selected pH range comprising forming a mixture of said agent with a pharmaceutically acceptable liquid, said mixture having a pH outside said selected range, and contacting said mixture with proteinoids formed of thermal condensation polymers of mixed amino acids which are soluble within said selected pH range and insoluble in said mixture to form microspheres having diameters less than 10 µm containing the active agent.

13. Method for producing an orally administrable composition for delivering insulin to the blood

stream in physiologically active form comprising mixing insulin with water and contacting said mixture with a thermal condensation polymer derived from two parts glutamic acid, two parts aspartic acid and one part neutral or basic alpha-aminoacid."

Claims 2 to 9 were dependant to claim 1. Claims 11 and 12 were dependent on claim [12](sic!).

II. The Examining Division considered document;

(1) EP-A-0 000 667

to be relevant to the question of novelty (Article 54 EPC) for the following reasons:

Several references to the description of document (1) demonstrated that a pharmacologically active agent had been encapsulated within a protenoid microsphere of diameter less than 10µm formed from thermal condensation polymers of mixed amino acids and that release of active ingredient from the said microcapsule would be within the normal pH range of blood. Since all such features were to be found in document (1) the subject-matter of claim 1 of the application was anticipated and thus not novel as required by Articles 52(1) and 54 EPC.

With regard to inventive step required by Article 56 EPC this could not be recognised as there was no evidence of an unexpected or unobvious effect. Further to this the applicant had obviously made use of known properties of known matrix materials. No

inventive features were recognised for the dependant claims and further independant claims.

Additional arguments brought forward by the applicant were meaningless because their significance was not reflected in the claims and in particular the fact that in document (1) magnetic particles were embedded in the microsphere matrix was irrelevant as this was encompassed by the claim wording.

The requirements of Article 123(2) EPC were said to be met.

Claims 2 to 4 and 8, however, were considered not to comply with the requirements of Article 84 EPC for reasons stated in the first communication. These were that

(a) Claim 2 did not give a technical teaching how to act, instead it consisted of desired results to be achieved, without any indication how to achieve the said results;

(b) Claims 3 and 4 comprised all possibilities without any preference and reflected inherent properties described as known and were therefore trivial;

(c) Claim 8 was not concise and therefore did not meet the requirements of Article 84 EPC.

III. The Appellant lodged an appeal, paid the appeal fee and filed a statement of grounds for the appeal. A

new set of claims 1 to 13 was filed, there being amendments to claims 2, 8, 11 and 12, merely relating to the Article 84 EPC objections and inaccurate dependency.

The Appellant maintained that the subject-matter of the claims was novel and inventive having regard to document (1). There it was not taught that the protenoid microspheres released said pharmacological agent within a selected pH range. The microspheres of the invention were administered orally, could be formulated to be stable at acidic or basic pH values and to degrade and release the pharmacologically active reagent at another pH value. In particular this enabled protenoids stable to stomach acids to be used for encapsulation of pharmacological agents which were released other than in the stomach at neutral or basic pH values. The application also described basic and neutral microspheres and methods for their manufacture. On the other hand document (1) described microspheres which were intravascularly administrable, magnetically localisable, biodegradable carriers of an amino acid polymer matrix with magnetic particles therein. This matrix could also entrap therapeutic and diagnostic agents and was used to deliver such substances intravascularly to a selected site under an applied magnetic field.

Further document (1) related only to microspheres of homopolymers of amino acids which relied upon enzyme action for release of the active agent and did not disclose that the polymer matrix was made from a

mixture of amino acids which was obligatory for the microspheres of the invention and which enabled the control of pH for release of the active ingredient to be achieved.

Whereas the application in suit described an encapsulation process document (1) did not relate to a genuine encapsulation of the pharmacologically active agent as the product was a drug impregnated spherical matrix prepared by (a) formation and loading and (b) a fixation process to fix the drug cargo in place. The evidence for this was that the microspheres of document (1) could be loaded either during the formation of the matrix solution or after formation. If a true encapsulation had taken place then the pharmacological agent could not be loaded after matrix solution formation. Since the drug impregnated the microspheres of document (1) it could flow in and out of the spherical matrix and therefore had to be fixed by denaturing the protein matrix either chemically or thermally. The microsphere of the application did not require fixation or denaturing of the protein as true encapsulation had been carried out.

It was the purpose of the disclosure of document (1) to provide a microsphere which contained magnetic particles for the subsequent targeting process using a magnetic field and although example VI omitted the magnetic particles there was no disclosure as to how such a microsphere may have been employed.

IV. The written submissions imply that the Appellant

requested that the decision of the Examining Division be set aside and that a patent be granted on the basis of claims 1 to 13 submitted on the 12 December 1992, or as auxiliary request the application be referred back to the first instance.

Reasons for the Decision

1. The appeal is admissible.

2. *Clarity, (Article 84 EPC)*

The claims of the new request now on file, submitted on 12 December 1992 and which took into account the lack of clarity objections raised by the Examining Division in its decision relating to claims 2 to 4 and 8 are now clear and do not contravene the requirements of Article 84 EPC.

3. *Article 123(2) EPC*

The claims of the new request do not contravene Article 123(2) EPC because the amendments to claims 2 and 8 are based on the originally filed PCT application at page 5 lines 13 to 19 and the remaining amendments to claims 11 and 12 constitute correction of inaccurate dependancy.

4. *Novelty, (Article 54 EPC)*

4.1 Document (1) discloses an intravascularly-administrable and magnetically-localisable

biodegradable carrier, comprising microspheres formed from an amino acid polymer matrix with magnetic particles embedded therein, the microspheres having a number average size of less than 1,5 µm. The microsphere may be prepared from a single amino acid polymer or from a mixture of such polymers and may contain a pharmacologically active agent. In the description at page 4 lines 26 to 29 it is disclosed that the active agent is "dissolved or dispersed in the matrix material during the formation of the microspheres". The product of example VI is an amino acid polymer carrier matrix prepared from albumin which does not include magnetic particles.

4.2 In claim 1 of the present application a pharmacologically active material is claimed encapsulated within proteinoid microspheres having diameters less than 10 µm and formed from thermal condensation polymers of mixed amino acids, the nature and proportions of the amino acids being chosen such that the microsphere will dissolve at a desired pH value thus releasing the active material.

4.3 A comparison of the subject matter of claim 1 with that of document (1) gives rise to the following differences in technical features of the separate microspheres:

(a) The microspheres of the application are in the form of a hollow capsule within which the active ingredient is contained, whereas those of the prior art are solid spheres comprising a polymer matrix.

(b) The active ingredient is encapsulated within the hollow microspherical shell of the application and is not contained in the shell material. Microspheres of the prior art have the active ingredient dissolved or dispersed throughout the solid sphere. The word "encapsulated" has been incorrectly used in document (1) because it is only applicable to products having an outer shell thus forming a capsule which is technically not the case in document (1), and this has confused the nature of the microspheres of that document.

(c) The pH sensitivity of the microspheres of the application is created by polymerising together mixed amino acids in required proportions to give reactivity at pH values existing at the proposed site of treatment. This is not a feature of the prior art microspheres.

(d) Microspheres of the invention are sealed by the encapsulation process whereas those of document (1) are not and require after-treatment to avoid loss of pharmacologically active material.

(e) The microspheres of the invention are prepared by a thermal condensation process.

4.4 Features (a) to (e) give rise to technical differences of the microspheres and are the reasons why the subject-matter of the main claim is novel and complies with Article 54 EPC. The above differences

from the prior art apply to the subject-matter of claims 2 to 9, which are dependant to claim 1, and thus these claims also relate to novel subject-matter.

4.5 Independant claim 10 relates to a method for producing microspheres and method claims 11 and 12 referring to preferred procedural features are dependant to claim 10.

Document (1) prepares microspheres by emulsifying an aqueous solution of matrix material containing therapeutic or diagnostic agent either dissolved or in particulate form with an oil. The aqueous phase at the time of addition of the oil also contains magnetic particles.

Microspheres according to the method of claim 10 of the application are prepared by mixing a pharmacologically active agent for target release within a selected pH range with a pharmaceutically acceptable liquid, the pH thereof being outside the target release pH range, this mixture then being contacted with proteinoids formed of thermal condensation polymers of mixed amino acids which are soluble within the target release pH range but insoluble in the said mixture to form microspheres. This process differs from that of document (1) in that (a) the pharmaceutically active material is not first mixed with the matrix material but with a pharmaceutically acceptable liquid, (b) this mixture is then added to the pH sensitive proteinoid polymer of mixed amino acids (c) which are thermally

condensed and (d) no oil is used to form an emulsion from which microspheres are obtained. The method of claim 10 and of the two dependant claims 11 and 12 is for reasons (a) to (d) novel.

4.6 Independant claim 13 represents a specific method for producing an orally administrable composition containing insulin by mixing insulin with water and contacting it with a specific thermal condensation polymer derived from a combination of two parts of each of glutamic and aspartic acids and one part of neutral or basic alpha-aminoacid. This method is analogous to that of claim 10 and this subject-matter is therefore also novel.

5. *Inventive step, (Article 56 EPC)*

5.1 The closest prior art is document (1) and the differences between the disclosure of that document and the claimed subject-matter are given above in paragraph 4.3. Further document (1) discloses at page 2 lines 1 to 4 the effective intravascular delivery of therapeutic agents to a selected organ site by the provision of microspheres containing magnetic particles which enabled said spheres to be moved to a chosen site by application of a magnetic field after intravascular injection of the preparation containing the spheres.

5.2 The technical problem

On the basis of the disclosure of document (1) the problem to be solved can be seen in the provision of

an alternative method for supplying a pharmacologically active agent to a target organ in a body where the agent is then released.

5.3 Assessment of inventive step

The relevant question for assessment of inventive step is whether it was possible for the skilled person to obviously derive from document (1) those features which distinguish the subject-matter of claim 1 from it and which enable oral administration and subsequent release of the pharmacological agent at the desired site without the more onerous application of magnetic microspheres.

There is no teaching in document (1) which obviously leads to those features stated in paragraph 4.3 which distinguish the microspheres of the present application from those of the prior art because there is no suggestion of pH-sensitive microspheres nor of the method by which they are made. A water-oil emulsion system as employed in the process of document (1) does not lead the skilled person to employ the encapsulation process of the invention in which an aqueous mixture of pharmacologically active agent is employed in combination with mixed amino acids prepared by thermal condensation to form hollow spheres and to determine pH sensitivity of the microsphere produced. The encapsulation of the pharmacologically active agents in microspheres which are pH-sensitive within a selected pH range is based upon the technical process feature that encapsulation is directly possible by dissolving or suspending the

active agent in a pharmaceutically acceptable liquid which interacts with a proteinoid formed from mixed amino acids by thermal condensation to form microspheres, (paragraph bridging pages 5 and 6 of the PCT application).

Although it is also possible to administer pH-neutral microsphere preparations of the invention by intravenous injection, these preparations are stable in the bloodstream and only release their active agent in the environment of the target organ at pH values different from neutral pH or in response to an enzyme, (page 7 lines 20 to 25 of the PCT application). In this latter respect the microspheres of the invention appear to function in the same way as those of document (1) which contain magnetic particles, however the pH-sensitve microsphere of the application is per se inventive and distinguished from the magnetic particle free microsphere of example VI of document (1), for which no use was given, by virtue of the technical features referred to in paragraph 4.3 above.

The technical features of the process claimed in claims 10 and 13 solve the problem as specified in paragraph 5,2 above and are inventive for the same reasons which led to acknowledgement of inventive step of claim 1.

For these reasons the pH-sensitive microspheres of the main claim and of the dependant claims 2 to 9 as well as the microencapsulating method of claims 10 to 12 and the method of claim 13 for producing an orally

administrable insulin composition, all filed on 12 December 1992 are considered to be inventive, and accordingly the requirements of Article 56 EPC are met.

Order

For these reasons it is decided that:

1. The decision of the Examining Division is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of the request filed on 12 December 1992.

The Registrar: The Chairwoman:

L. McGarry U. M. Kinkeldey.