(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 March 2009 (19.03.2009)

PCT

(10) International Publication Number
WO 2009/034453 A4

(51) International Patent Classification:
A61K 9/06 (2006.01) *A61K 9/00* (2006.01)
A61K 38/28 (2006.01) *A61K 9/20* (2006.01)
A61K 47/32 (2006.01)

(21) International Application Number:
PCT/IB2008/002368

(22) International Filing Date:
12 September 2008 (12.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P07 01 04071 13 September 2007 (13.09.2007) AR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: METHOD FOR THE IMMOBILIZATION OF BIOACTIVE MOLECULES WITHIN A POLYMERIC SUBSTRATE RESISTANT TO THE STOMACH ACIDS AS ORAL DRUG DELIVERY SYSTEM

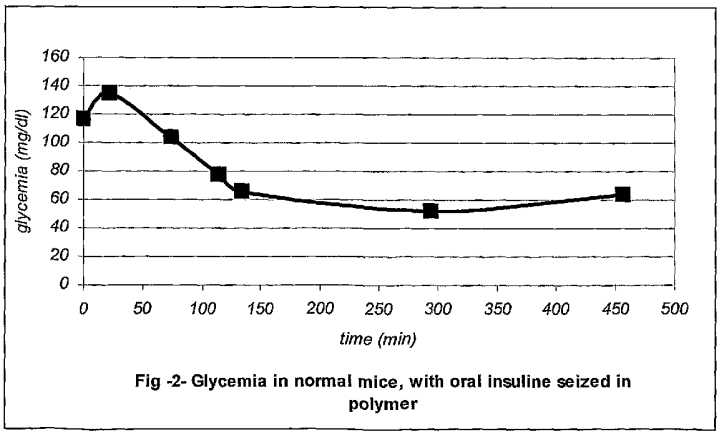

Fig -2- Glycemia in normal mice, with oral insuline seized in polymer

(57) Abstract: It is described a technology which allows to surpass the gastric barrier for proteic compounds administrating bioactive molecules, particularly insulin. It is proposed a method to replace the daily repetitive injectable doses of insulin by a product oralyy administered. It is characterized by the following steps: a) mix at least a monomer suitable for polymerization by means of a ionizing radiation, with at least an aqueous solution of bioactive molecules; place the thus obtained mixture in step (a) into a resistant container permeable to said ionizing radiations; submit said container to a flow of ionizing radiation at a dose capable to polymerize all the monomer, in a dose range from 0.1 kGy up to 50 kGy, particularly in a 5 to 30 kGy in range, obtaining within the container a polymer resistant to the stomach acids. And the polymer containing in its nanotubules bioactive molecules; withdraw the thus polymer obtained in step (c), and dividing it in batches with a size range of 1 mm x 1 mm x 1 mm up to 8 mm x 8 mm x 8 mm, It is an objective of this invention. A method for the introduction of bioactive molecules in a polymeric substrate resistent to the stomach acids, to be employed as a retarding orally administered medicine, being these molecules insulin which is releaase directly to the liver being the liver its first action site, through the portal

[Continued on next page]

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— *with amended claims and statement (Art. 19(1))*

(88) Date of publication of the international search report: 14 January 2010

Date of publication of the amended claims and statement: 29 April 2010

circulation; an orally relased insulin of delayed action by means of which, when the insulin is released into the liver, controls the porduction of hepatic glucose; an orally relased insulin of delayed action by means of which eht einsulin does not produce peaks in the systemic circulation, as it does with the injectable insulin, reducing the risks of the sudden descrese in the glucemia levels, an orally adminstered mediciene with a prolongued retared effect, by means of wish it is neccesary a lesser insulin dose.

We claim

1. Method for the inmobilization of bioactive molecules within a polymer substrate to be employed as an oral drug delivery system, comprising:
a water insoluble but water swellable carrier matrix, incorporating the biologically active agents, where the matrix is a macromolecular network synthesized by gamma radiation at temperatures well below zero degree centigrade.

2. The method according to claim 1, where the polymer substrate is a hydrogel.

3. The method according to claim2, where the hydrogel is not biodegradable but it is biocompatible.

4. The method according to claim 1, where, initially before irradiation, DDSystem is an aqueous solution containing the bioactive molecules, mixed with the monomer components of the matrix and free radical scavengers.

5. The method according to claim 4, where the macromolecular network obtained after the radiation treatment is a porous substrate comprising a homopolymer or a copolymer prepared from one or more monomers selected from the group consisting of alkyl-methacrylates and acrylates.

6. The method according to claim 4, where the radiation treatment is from gamma radiation sources in a dose range from 0.1 kGy to 50 kGy (kiloGray), particularly in a 5 to 30 kGy dose range.

7. The method according to claim 4 where the radiation treatment is from electron beams or bremsstrahlung(braking radiation) therefrom with energy between 0.1 MeV and 7 MeV

8. The method according to claim 7, in a dose range from 0.1 kGy to 50 kGy (kiloGray), particularly in a 5 to 30 kGy dose range.

9. The method according to claim 1, where the temperature of the radiation treatments is well under freezing temperature, namely at glass state temperature.

10. The method according to claim4, where the bioactive molecule is insulin and the free radical scavengers is glycerin.

11. The polymer substrate according to claim1, can be obtained in any shape and quantity and loaded with different amounts of bioactive molecules.

12. The polymer substrate according to claim 1, as a therapeutic-containing carrier can be subdivided and combined in different sizes containing each different amounts of the bioactive molecules.

STATEMENT UNDER ARTICLE 19 (1)

The documents cited in the international search report where considered appropriate for the general discussion.

All cited documents (D1-D5) considered quite different matrix fabrication:
D1 to D3 involves ultraviolet photopolimerization
D4 and D5 involve chemical polymerization.

Both processes incorporates additional chemicals considered contaminants:
Photoinitiators (uranyl nitrate, DMPA, IRACURE 2959, TMED, (NH4)2 S2O8) Crosslinkers (EGD, PEG200DMA, PEG400DMA,, N,N-methylene-bisacrylamide),
Preservatives (Thiomersalate, IDA).

The temperature of the different matrix fabrication systems (D2-D5) are conducted at normal or higher temperature values with different method for drug incorporation (imbibition).
The exception is D1 which employs the "Freeze-thaw polymerization matrix fabrication" where the temperature of the polymerization is under zero but widely variable.

We consider that our presentation have novelty and inventive step in providing a simpler method for the preparation of a DDS consisting in a unique procedure comprising irradiating the complete therapeutic solution without contaminants, with high energy radiation sources at glass temperature.

We agreed the text established by the Authority to read as follow: Method for the immobilization of bioactive molecules within a polymeric substrate resistant to the stomach acids as oral drug delivery system.