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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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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(54) Title: MICROSPHERE FORMULATIONS COMPRISING MULTIPLE NON-IDENTICAL PEPTIDES AND METHODS FOR MAKING THE SAME

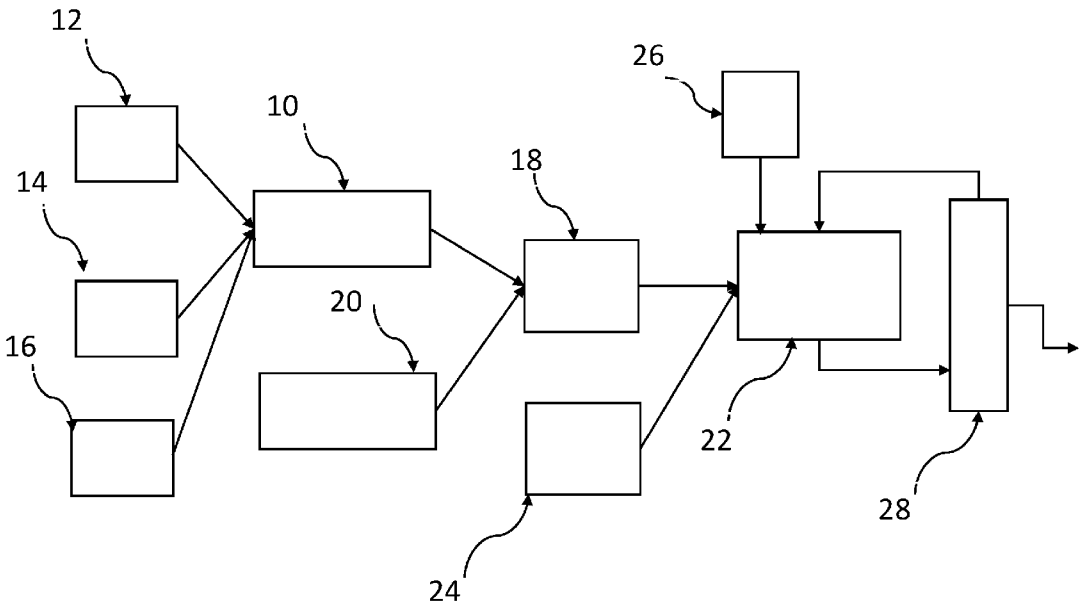

FIG. 1

(57) Abstract: A microsphere formulation comprising polymer microspheres is provided, each polymer microsphere comprising: at least two non-identical peptides; and a biodegradable polymer, wherein each polymer microsphere has a drug load of at least about 0.15 wt/wt% of each of the non-identical peptides, and wherein the polymer microspheres have an average particle size of less than about 12.6 μM (D_{50}). The polymer microspheres may further comprise an adjuvant. Methods for making and using the microsphere formulations are also provided.

[Continued on next page]

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GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

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26 January 2023 (26.01.2023)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/71868

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 9/16 (2022.01)
ADD. A61K 47/34; B01J 13/02 (2022.01)

CPC - INV. A61K 9/1623; A61K 9/1647; A61K 9/1694
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/155396 A1 (DR. REDDY'S LABORATORIES LIMITED) 15 August 2019; Page 22, third paragraph	1st invention: 1-3, 16, 17, 18/16, 18/17 // 2nd invention: 1-3, 16, 17, 18/16, 18/17 // 3rd invention: 1-3, 16, 17, 18/16, 18/17
Y	WO 2011/039337 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.) 07 April 2011; Claim 9	1st invention: 17, 18/17 // 2nd invention: 17, 18/17 // 3rd invention: 17, 18/17
Y	WO 2005/103259 A1 (UNIVERSITY HEALTH NETWORK et al.) 03 November 2005; 1st invention: page 32/89 // 2nd invention: page 60 // 3rd invention: page 62	1st invention: 1-3, 16, 17, 18/16, 18/17 // 2nd invention: 1-3, 16, 17, 18/16, 18/17 // 3rd invention: 1-3, 16, 17, 18/16, 18/17
Y	US 8,895,033 B2 (HOUCHIN, ML et al.) 25 November 2014; Abstract; column 8, lines 20-36; column 9, lines 56-58; column 10, lines 35-45; column 10, lines 35-45 and 63-67; column 11, lines 1-13; claim 1	1st invention: 1-3, 16, 17, 18/16, 18/17// 2nd invention: 1-3, 16, 17, 18/16, 18/17// 3rd invention: 1-3, 16, 17, 18/16, 18/17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2022 (26.09.2022)	NOV 14 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-15, 22-24
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
-***-Please See Supplemental Page-***-

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1st invention: Groups I+, claims 1-3, 16-18 SEQ ID NO: 1 (insertion sequence).
2nd invention: Groups I+, claims 1-3, 16-18 SEQ ID NO: 2 (insertion sequence).
3rd invention: Groups I+, claims 1-3, 16-18 SEQ ID NO: 3 (insertion sequence).

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/71868

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. CHANDIRAN ET AL. "Preparation and evaluation of aceclofenac loaded biodegradable microspheres" 1-5. International Journal of PHARMACEUTICAL AND BIOMEDICAL RESEARCH, ISSN NO: 0976-0350. Web. 24 February 2010; Fig. 1; page 21, second column, third paragraph	1st invention: 1-3, 16-18 // 2nd invention: 1-3, 16-18 // 3rd invention: 1-3, 16-18
Y	US 2006/0177458 A1 (KENSIL, CA) 10 August 2006; Title; claim 1	1st invention: 1-3, 16, 17, 18/16, 18/17 // 2nd invention: 1-3, 16, 17, 18/16, 18/17 // 3rd invention: 1-3, 16, 17, 18/16, 18/17
A	N. KAMALY ET AL.. "Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release." pages 2602-2663. Chemical reviews. Vol. 116, No. 4. 24 February 2016; entire document; DOI: 10.1021/acs.chemrev.5b00346	All inventions: 1-3, 16-18

-***-Continued From Box No. III: Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, claims 1-3, 16-18 SEQ ID NO:1 (insertion sequence) is directed to a microsphere formulation comprising polymer microspheres comprised of nonidentical peptides, biodegradable polymers, and adjuvants.

Group II, claims 19-21, is a method for making a microsphere formulation comprising contact in an organic solvent, formation of an emulsion, and formation and subjection of an organic solvent-free microsphere to freeze drying.

The formulation of Claims 1-3, 16 (in-part), and 17-18 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they comprise an insertion sequence encompassing SEQ ID NO: 1 (first exemplary insertion sequence).

Applicant is invited to elect additional insertion sequences, with specified SEQ ID NO: for each, to be searched. Additional sequence(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be SEQ ID NO: 2 (insertion sequence).

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

No technical features are shared between the insertion sequences of Groups I+, accordingly, these groups lack unity a priori.

Furthermore, the inventions listed as Group I+ and Group II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I+ include polymer microspheres with drug loads and average particle size of less than 12.6 micromolar, not present in Group II; and the special technical features of Group II include contacting, in an organic solvent, combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion, removing the organic solvent, and subjecting the substantially organic solvent-free microsphere formulation to freeze-drying, not present in Group I.

Group I and Group II are considered to share the technical features including: nonidentical peptides, adjuvants, and biodegradable polymers.

These shared technical features are previously disclosed by the publication entitled "Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release" by Kamaly, et al. (hereinafter "Kamaly").

Kamaly discloses that the development of biodegradable polymers represents a revolution in medicine spanning over 50 years and leading to significant biotechnological advancements in drug delivery, biomaterials, tissue engineering, and medical device development while bringing together chemists, engineers, biologists, and physicians in a unique and collaborative manner (Introduction). Kamaly further discloses that the time frame of this revolution mirrors discoveries of more potent therapeutics in the form of peptides, proteins, nucleic acids, and other bioactive molecules. (Introduction). Kamaly also discloses that SEL-068 is a first-in-class synthetic and integrative targeted polymeric NP vaccine that is fabricated using degradable PLGA and PLA–PEG polymers and contains nicotine as antigen, T-helper-cell peptides, and TLR agonists as adjuvants (page 18). Since Kamaly discloses the use of biodegradable polymers, potent therapeutics in the form of peptides, and synthetic and integrative targeting polymeric NP vaccine that is fabricated using degradable polymers and TLR agonists as adjuvants, it would have been obvious to one of ordinary skill of the art to arrive to the shared technical features of nonidentical peptides, adjuvants, and biodegradable polymers in the instant application.

Since no special technical feature of the Group I+ and Group II Inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Kamaly reference, unity of invention is lacking.