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(54) Title: TOPICAL OCULAR DELIVERY OF CROMAKALIM

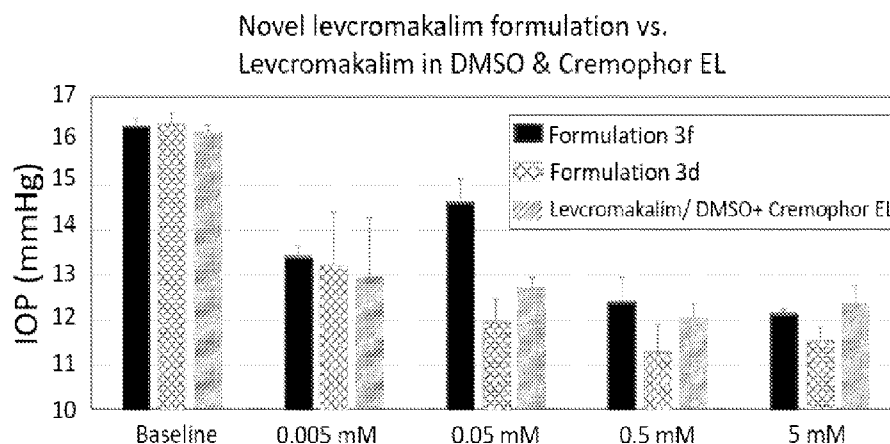


FIG. 3

(57) Abstract: Aqueous ocular topical pharmaceutical formulations are provided that deliver an effective amount of (lev)cromakalim or a pharmaceutically acceptable salt thereof to treat an anterior or a posterior ocular disorder that responds to (lev)cromakalim, including glaucoma, as well as diseases where the further lowering of intraocular pressure is beneficial to reducing disease progression.



LU, LV, MC, ME, 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).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

(88) Date of publication of the international search report:

04 July 2024 (04.07.2024)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/78754

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/4025 (2023.01)

ADD. A61K 9/08; A61K 47/10; A61K 47/38; A61K 47/44; A61P 27/02 (2023.01)

CPC - INV. A61K 31/4025

ADD. A61K 9/08; A61K 47/10; A61K 47/38; A61K 47/44; A61P 27/02

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 database consulted during the international search (name of database 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.
X --- Y --- A	WO 2021/158992 A1 (MAYO FOUND MEDICAL EDUCATION & RES) 12 August 2021; Fig. 5A; pg. 9 lines 26-28; pg. 10 lines 1-3, 20-30; pg. 16 lines 8-12; pg. 35 lines 14-16; pg. 83 lines 16-19; pg. 84 lines 7, 10-20; pg. 85 lines 2-4; Claim 23	1-10, 49-50, 87 --- 53-55, 58-63, 64/62, 64/63, 79-82 --- 51-52, 56-57, 77-78, 83, 88-104, 109, 144-146
Y --- A	WO 2021/213512 A1 (GUANGZHOU KANGRUI BIOLOGICAL PHARMA TECH CO LTD) 28 October 2021; paragraphs [0026], [0029], [0130], [0215], [0300], [0458], [0499]; Claim 39	53 --- 1-10, 49-52, 56-57, 77-78, 83, 87-104, 109, 144-146
Y --- A	WO 2022/207773 A1 (ACTIVE BIOTECH AB) 06 October 2022; pg. 12 lines 20-21; pg. 19 lines 10-15; pg. 20 lines 25-26; pg. 25 lines 1-5, line 32 - pg. 26 line 2; pg. 30 lines 17-21; pg. 65 lines 21-23	54-55, 58-63, 64/62, 64/63, 79-82 --- 1-10, 48-53, 56-57, 77-78, 83, 87-104, 109, 144-146
A	US 2020/0306218 A1 (AERIE PHARMA INC) 01 October 2020; paragraph [0100]	1-10, 49-64, 77-85, 87-104, 109, 144-146
A	US 2014/0206626 A1 (SAINT REGIS MOHAWK TRIBE) 24 July 2014; paragraph [0103]	1-10, 49-64, 77-85,

☒ 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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/78754

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2021/0299046 A1 (RHODES TECHNOLOGY RHODE ISLAND) 30 September 2021; Table 14; paragraph [0193]	87-104, 109, 144-146 1-10, 49-64, 77-85, 87-104, 109, 144-146
A	US 2019/0060397 A1 (SUN PHARMA IND LTD) 28 February 2019; Abstract; paragraph [0040]	1-10, 49-64, 77-85, 87-104, 109, 144-146

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/78754

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.: 11-48, 65-76, 86, 105-108, 113-143, 147-164
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.:
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.:
1-10, 49-64, 77-85, 87-104, 109, 144-146

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/US23/78754

-***-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.

Group I – claims 1-10, 49-64, 77-85, 87-104, 109, 144-146 are directed toward an ocular topical formulation and a pharmaceutical composition.

Group II – claims 110-112 are directed toward an ocular topical formulation which does not include DMSO, DMF, NNIP or any unacceptable topical carrier.

The inventions listed as Groups I and 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 an ocular topical formulation, wherein the ocular topical formulation is stable at ambient conditions for at least 4 months and comprises three or more components selected from the group consisting of a. a polyol; b. a polyethoxylated furanose fatty acid ester; c. a nonionic tri-block copolymer of a central hydrophobic chain of polyoxypropylene flanked by two hydrophilic chains of polyoxyethylene (poloxamer); d. a polymeric alkyl or aryl polyol; e. an ethoxylated glycerol ester; f. a polymeric lactam; g. hydroxyalkyl cellulose; h. an oil in water polymeric emulsifier of a block copolymer of polyacrylic acid and a hydrophobic C10-C30 alkyl acrylate; and i. an ethoxylated alkylphenol; in an aqueous formulation with a pH from about 6 to about 8; a formulation which comprises three or more components selected from the group consisting of glycerin, polysorbate 80, poloxamer 407 or Pluronic® F127, tyloxapol, Kolliphor® ELP, Kolliphor® RH 40, Kolliphor® HS 15, hypromellose, PVP, Premulen 1M TR-1 or Premulen TM TR-2, and octoxynol-40; a formulation comprising polyvinylpyrrolidone (PVP), mannitol, water, and phosphate buffer; a formulation which comprises polyvinylpyrrolidone (PVP) K-30 with a pH of about 6.5; a formulation which has a concentration of (lev)cromakalim or a pharmaceutically acceptable salt thereof of up to about 5 mM; a formulation which has a concentration of (lev)cromakalim or a pharmaceutically acceptable salt thereof, which comprises glycerin, hypromellose; a pharmaceutical composition; a formulation which has a concentration of (lev)cromakalim or a pharmaceutically acceptable salt thereof of about 0.4 mM; a formulation which has a concentration of (lev)cromakalim or a pharmaceutically acceptable salt thereof of about 0.8 mM; a formulation which has a concentration of (lev)cromakalim or a pharmaceutically acceptable salt thereof of about 2 mM; a formulation comprising (lev)cromakalim or a pharmaceutically acceptable salt thereof (0.015% w/v), Kolliphor® ELP (4% w/v), polysorbate 80 (1% w/v), polyvinylpyrrolidone (PVP) K-30 (2% w/v), poloxamer 407 (0.1% w/v), mannitol (3.3% w/v), sodium phosphate dibasic buffer, sodium phosphate monobasic buffer, and water; a formulation comprising (lev)cromakalim or a pharmaceutically acceptable salt thereof (0.03% w/v); and a formulation comprising (lev)cromakalim or a pharmaceutically acceptable salt thereof (0.075% w/v), not present in Group II; the special technical features of Group II include a formulation without significant crystallization or undue separation of cromakalim from the liquid and does not include DMSO, DMF or NNIP or other unacceptable topical carrier for human use and has at least two excipients, not present in Group I.

Groups I and II share the technical features including: a ocular topical formulation that can be used as an eye drop comprising between about 0.05 mM to about 5 mM of (lev)cromakalim, or a pharmaceutically acceptable salt thereof, in an aqueous liquid that is stable under ambient conditions for at least five months.

However, these shared technical features are previously disclosed by the publication "Ocular Hypotensive Effects of the ATP-Sensitive Potassium Channel Opener Cromakalim in Human and Murine Experimental Model Systems" by CHOWDHURY, UTTIO ROY et al. (hereinafter 'CHOWDHURY') in view of US 2013/0023550 A1 to GLAXO WELLCOME MANUFACTURING PTE, LTD (hereinafter 'GLAXO').

CHOWDHURY discloses an ocular topical formulation that can be used as an eye drop comprising between about 0.05 mM to about 5 mM of (lev)cromakalim, or a pharmaceutically acceptable salt thereof (a bolus of 5 mM cromakalim was added topically to one eye daily for 5 consecutive days; the PCT Instant Application teaches that the parent cromakalim drug and levromakalim are referred to together as (lev)cromakalim on page 6 lines 18-19; page 3 paragraph 2). CHOWDHURY does not disclose an eye drop which comprises an aqueous liquid that is stable under ambient conditions for at least five months. GLAXO discloses an eye drop which comprises an aqueous liquid that is stable under ambient conditions for at least five months (a pharmaceutical composition comprising water, which is stable for at least 12 months, which is an eye drop; claims 1, 12-13). It would have been obvious to one of ordinary skill in the art, before the relevant date, to modify the formulation of CHOWDHURY to include an eye drop which comprises an aqueous liquid that is stable under ambient conditions for at least five months, as taught by GLAXO, because GLAXO teaches a formulation which can treat ocular disorders with sufficient stability to allow for the dosage forms to be manufactured, delivered, dispensed, and administered by the patient for the entire course of treatment for the given prescription, which could take a year or more (GLAXO; paragraphs [0010]-[0011]).

Since none of the special technical features of the Groups I and II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the CHOWDHURY and GLAXO references, unity of invention is lacking.