

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IN2023/050790

International filing date (day/month/year)
22.08.2023

Priority date (day/month/year)
08.06.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/51 A61K31/337 A61L31/16 A61K9/00

Applicant
SAHAJANAND MEDICAL TECHNOLOGIES LIMITED

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43 <i>bis</i> .1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Konter, Jörg

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>17</u>
	No: Claims	<u>1-16, 18-22</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference

Reference is made to the following documents:

- D1 CN 114 796 811 A (INST METAL RESEARCH CAS ET AL.) 29 July 2022 (2022-07-29)
- D2 CN 104 523 595 A (SHENZHEN INST OF ADV TECH CAS) 22 April 2015 (2015-04-22)
- D3 CHAN J M ET AL: "PLGA-lecithin-PEG core-shell nanoparticles for controlled drug delivery",
BIOMATERIALS, ELSEVIER, AMSTERDAM, NL,
vol. 30, no. 8, 1 March 2009 (2009-03-01), pages 1627-1634,
XP025876359, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.
2008.12.013 [retrieved on 2009-01-19]
- D4 US 2021/259976 A1 (WANG LIXIAO [US] ET AL) 26 August 2021 (2021-08-26)
- D5 VARGHESE SEBY ELSY ET AL: "Lecithin and PLGA-based self-assembled nanocomposite, Lecithmer: preparation, characterization, and pharmacokinetic/pharmacodynamic evaluation",
DRUG DELIVERY AND TRANSLATIONAL RESEARCH, SPRINGER, GERMANY, vol. 6, no. 4, 1 July 2016 (2016-07-01), pages 342-353,
XP035998994, ISSN: 2190-393X, DOI: 10.1007/S13346-016-0314-Y
[retrieved on 2016-07-01]
- D6 Du Ruolin ET AL: "Design and testing of hydrophobic core/hydrophilic shell nano/micro particles for drug-eluting stent coating",
NPG Asia Materials, vol. 10, no. 7, 1 July 2018 (2018-07-01), pages 642-658,
XP055950440, ISSN: 1884-4049, DOI: 10.1038/s41427-018-0064-z Retrieved from the Internet:
URL:<https://www.nature.com/articles/s41427-018-0064-z.pdf>

Machine translations of D1 and D2 are enclosed to this communication.

2. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-16, 18-22 is not new in the sense of Article 33(2) PCT.

2.1 Document D1 (CN114796811; examples 1-3; claims 1-10; figures 1,2; paragraphs after the "Summary of the Invention") discloses a drug coated balloon device. The coating comprises nanoparticles (200-400nm) comprising the mass concentration of lecithin 5%-20%, and the mass ratio of each material is lecithin:drug=5:1-1:5; (lecithin+drug):PLGA = 20:1 to 1:1. PLGA serves as sustained release core material. The drug loading dose of the drug-coated balloon is 1-2 µg/cm. The drug is paclitaxel. Preparation by preparing a single solution which is sprayed on the device.

The subject-matter of claims 1-14,16,18-20 is therefore not new over document D1.

2.2 Document D2 (CN104523595; example 2) discloses drug containing nanoparticles of 300nm comprising a PLGA core and a lecithin coating. Methods of preparation using acetonitrile as first solvent for the polymer and ethanol as second solvent for lecithin.

The subject-matter of claims 1-16, 18-20 is therefore not new over document D2.

2.3 Document D3 (Chan et al; figure 1; points 2.2, 3.3) discloses nanoparticles comprising docetaxel, PLGA cores and a shell of lecithin and DSPE-PEG. Methods of preparation using acetonitrile as first solvent for the polymer and ethanol as second solvent for lecithin.

The subject-matter of claims 1-16, 18-20 is therefore not new over document D3.

2.4 Document D4 (US2021259976; table 8) discloses a sample MSF13, MSF14 or MSF25-5, each comprising a PLGA core + phosphatidylcholin coating. Sirolimus as active agent.

The subject-matter of claims 1-16, 18-20 is therefore not new over document D4.

2.5 Document D5 (Varghese et al; page 344, paragraph spanning left column to right column; table 1) discloses nanoparticles comprising a PLGA core and lecithin shell. Trehalose as cryoprotectant.

The subject-matter of claims 1-16, 18-22 is therefore not new over document D5.

3. Inventive Step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-22 does not involve an inventive step in the sense of Article 33(3) PCT.

3.1 Lacking novelty, claims 1-16, 18-22 are not inventive.

3.2 Also document D6 (Du et al; figure 1) is relevant for inventive step and discloses nanoparticles comprising PLGA core and chitosan coating. Coating of stents for drug release.

Present claim 1 differs over D6 in that the primary peripheral excipient is made of phospholipid-based molecules.

There is no unexpected effect as a result of this difference. The examples are inconclusive with regard to this feature.

The problem to be solved is thus to provide an alternative nanoparticle for drug delivery.

Alternatively using a phospholipid based excipient is merely one of many options the skilled person would choose from in order to solve the problem posed. The cited prior art discussed above discloses phospholipid based coating on similar particles.

Accordingly, the claims are also not inventive in view of D6.

3.3 Any of D1-D6 may serve as closest prior art.

Present claim 17 differs over e.g. D2 in that the second solvent is methanol.

There is no unexpected effect as a result of this difference. The examples are inconclusive with regard to this feature.

The problem to be solved is thus to provide an alternative method for preparing nanoparticles for drug delivery.

Alternatively using methanol (instead of ethanol) is merely one of many options the skilled person would choose from in order to solve the problem posed. Methanol is a known alternative solvent to ethanol.

3.4 Should the Applicant recognize an improved effect over the prior art, the nature of the comparison with the closest state of the art must be such that said effect is **convincingly shown to have its origin in the distinguishing feature**. The discussion concerning this effect is to be based with **reference to the present application**, citing the appropriate passages.

Any reasoning for the presence of an inventive step should be given using the problem-solution approach.

According to the problem solution approach, all alternatives of a claim should solve the technical problem underlying the claimed invention.

In the present case, the examples demonstrate a characteristic release. However, this characteristic is primarily dictated by i) the nature of all constituents in the composition, ii) the amount of each constituent in the composition and iii) the method of manufacture of the composition. None of the claims disclose the features necessary to credibly achieve said characteristic release (Article 33(3) PCT).

Examples 1 and 2 of the application disclose specific formulations, comprising specific amounts of sirolimus (as the sole active) PLGA (as the only exemplified polymeric core), natural PC and PEGylated synthetic phospholipids (as the only exemplified phospholipid based molecules), with acetonitrile and methanol as the only exemplified solvents used in the specific manufacturing process.

The present claims are the maximum generalization of these examples.

In as far as there may be other solutions to the problem covered by the scope of the claims than those conceivable from a reasonable generalisation of the examples, these solutions must lack disclosure (Article 5 PCT) if one alleges that actually finding solutions to the underlying problem requires inventive skill in the first place. Evidently, if on the other hand that allegation was not correct, involvement of an inventive step could not be conceded even for the solutions demonstrated by the examples themselves (Article 33(3) PCT).

4. Industrial Applicability

The subject-matter of claims 1-22 meets the criteria for industrial applicability according to Article 33(4) PCT.

5. Further Remarks

It is noted that not all the legal frameworks of the PCT accept purpose limited entity claims, such as drafted in present claim 14.

Patentability, in particular novelty and inventive step, of claim 14 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D6 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

1. The application is using terms differently than what the skilled person would understand (Article 6 PCT).

According to claim 2, compounds such as lactose or glycol qualify as polymers, which they are not.

Claim 3 defines cholesterol to qualify as a phospholipid, which is not correct either.

Care shall be taken not to add subject-matter when overcoming this objection.

2. The term "about" used in the claims is vague and is not suitable to establish a distinguishable feature for the numerical values concerned over the prior art. This term should therefore be deleted. Any definition of the term "about" must be explicitly reflected in the claims in order to render its meaning clear from the wording of the claim alone.

Specifically, the definition provided by the application is different from what the skilled person would understand.

3. The term "particle size" used in claim 3 is vague and unclear, since it is strongly affected by the methods of determining as well as the measuring conditions (e.g. the apparatus) and therefore leaves the reader in doubt as to the meaning of the technical feature to which it refers, (Article 6 PCT).

Terms like "mean particle size or mean particle diameter", such as the arithmetic mean diameter (or count mean diameter), the volume or mass mean diameter, the mean surface area diameter belong to the most commonly used quantities for describing the average diameter of a particle population. The values of the average particle sizes of these methods differ for any particle size distribution. Hence there are different methods for determining the average/mean particle size yielding values for the same particle distribution which generally differ, under particular conditions by one or two orders of magnitude.

4. The parameter of claims 10-12 does not have an internationally accepted measurement method, although the measurement method affects the numeric value of the parameter, rendering the scope of protection sought unclear (Article 6 PCT).

5. The parameter of claims 18-19 does not have an internationally accepted measurement method, although the measurement method affects the numeric value of the parameter, rendering the scope of protection sought unclear (Article 6 PCT).

It is additionally not comprehensible what is meant. The Hansen solubility parameter is given for each molecule involved in a dissolution process, not only the solvent.

Specifically, each molecule is given three Hansen parameters, each generally measured in MPa^{0.5}:

- δ_d The energy from dispersion forces between molecules
- δ_p The energy from dipolar intermolecular forces between molecules
- δ_h The energy from hydrogen bonds between molecules.

6. Claims 20,21 discloses "further comprises a step of (...)"

However, claim 13, on which claims 20 and 21 depend, do not comprise any steps at all, rendering the phrase of claims 20 and 21 obscure (Article 6 PCT).

It is noted that claims 16-22 all depend on the entity claim 13. It is furthermore noted that this is not an obvious mistake, firstly because it is not immediately evident that a mistake occurred (i.e. the dependencies of claim 16-19 can be made sense of), secondly it is not evident what the obvious solution would be.

7. Claim 22 discloses "wherein the cryoprotectant is (...)". However, claim 13, on which claim 22 depends, does not disclose a cryoprotectant at all (Article 6 PCT).