BEFORE CONTROLLER OF PATENTS

THE PATENT OFFICE, KOLKATA

In the matter of Section 25(1) and Section 15 of The Patents Act, 1970 as amended by The Patents (Amendment) Act, 2005

And

In the matter of The Patents Rules, 2003 as amended by The Patents (Amendment) Rules 2020,

And

In the matter of: Patent Application No: 3140/KOLNP/2012.

APPLICANT: 1 . M/s. VERTEX PHARMACEUTICALS INCORPORATED.

OPPONENT : Mr. CHARANJIT KUMAR SEHGAL.

Present in hearing:

Hearing under Section 25(1) held on : 21st December 2018 through video-conference mode

For Applicant :

1. Ms. Archana Shanker –registered Patent Agent.
2. Mr. Devinder Singh Rawat- registered Patent Agent.

For Opponent :

3. NONE.

Hearing under Section 14 held on : 30th October 2019 through video-conference mode.

1. For applicant-Ms. Archana Shanker–registered Patent Agent.

DECISION

1. An application for a patent bearing number 3140/KOLNP/2012 was filed in Patent Office, Kolkata on 16th October 2012 entitled "SOLID FORMS OF (R)-1(2, 2-DIFLUOROBENZO[D][1,3]DIOXOL-5-YL)-N-(1-(2, 3-DIHYDEROXYPROPYL)-6-FLUORO-2-(1-HYDROXY-2-METHYLPROPAN-2-YL)-1-H-INDOL-5-YL) CYCLOPROPANECARBOXAMIDE". A request for examination under Section 11-B was filed on 14th March 2014 and was assigned a request no - 1051/RQ-KOL/2014. As per the provision under Section 11- A of the Patents Act (as amended), the said application was published on 21st June 2013.

2. The said application was examined according to the provisions in force of the Patents Act (as amended). A pre-grant opposition under Section 25(1) was filed by the opponent Mr. Charanjit Kumar Sehgal, having address at A – 204, Sunset 2, Raheja Vihar, Opp. Chandivali Studio Powai, Mumbai – 400073 on 25th March 2021 through a registered patent agent Chirag Tanna from Thane (W) , Maharastra. Notice under Rule 55 was issued to the applicant accordingly.

3. An interlocutory petition was filed by the applicant seeking therein to quash the pre-grant opposition under Section 25(1) as it has been filed by an IPR partner himself. The applicant also submitted other different grounds in their interlocutory petition.

4. The applicant further filed the reply in evidence on 18th August 2022. A pre-grant hearing was accordingly fixed and notice was issued to both the parties. The hearing was finally scheduled on 2nd November 2022.

5. The grounds of the opposition as adopted by the opponent in their pre-grant opposition was as follows-

    A. Section 25 (1) (e): that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any Inventive step.

    B. Section 25 (1) (f) : that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.

    C. Section 25(1)(g) : that the complete specification does not sufficiently and clearly describe the invention or method by which it is to be performed.

    D. Section 25(1)(h) : that the applicant failed to file or disclose information or furnishing false information relating to foreign filing.

6. <u>OPPONENT'S GROUNDS OF OPPOSITION:</u>

The following grounds were made by the opponent through their appointed patent agent in their pre-grant opposition -

A. <u>Under Section 25(1)(d):</u>

That the subject matter of the application is obvious in light of teachings of following:

• *US2009/131492,*

• *Yamashita et al, "Establishment of new preparation method for solid dispersion formulation of Tacrolimus", published in 2003.*

• *Kennedy et al., "Enhanced bioavailability of a poorly soluble VR1 antagonist using an amorphous solid dispersion approach: A case study", published in 2008.*

That US2009/131492 discloses compounds 315 and 322 in Table 1 which is the compound of present invention i.e. (R)-1(2,2-difluorobenzo[D][1,3]dioxol-5- yl)-N-(1-(2,3-dihyderoxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2- yl)-1H-indol-5-yl) cyclopropane carboxamide which is stated to be useful in treatment of cystic fibrosis. It also discloses the preparation of said compound and it is stated that the compound is obtained as a foamy solid i.e. as an amorphous solid. It further discloses that said compound can be used in solid dispersion comprising of a polymer, and which may further comprise of a surfactant.

Again Yamashita et. al. prepared solid dispersion formulations of a poorly soluble amorphous drug with different polymers namely PEG6000, PVP and HPMC. Yamashita and group found that the solid dispersion formulations prepared by using the polymer HPMC demonstrated highest increase in dissolution as well as bioavailability of the candidate drug. Yamashita states that HPMAC is considered one of the most suitable carriers for preparation of solid dispersion formulations among the polymers commonly known and used at the time of invention.

Further, Kennedy et. al have explored solid dispersion formulation of a poorly soluble drug which is prepared by spray drying using a combination of HPMC, hydroxypropyl methylcellulose and HPMCAS, hydroxypropyl methylcellulose acetate succinate. Kennedy and group found that combination of HPMC polymer along with a variant of HPMC which is enteric polymer i.e. HPMCAS results in significant improvement in maintenance of the drug in amorphous form during stability as well as significantly enhanced bioavailability of the drug in solid dispersion as compared to the amorphous drug which is not present as a solid dispersion. From the data of the prior art documents it has been explicitly established that solid dispersion formulations of poorly soluble drugs comprising HPMC and HPMCAS polymers wherein the drug is in substantially amorphous form and which exhibit better dissolution and bioavailability as compared to the amorphous drug were already available in the field at the priority date of the impugned application. Hence, the claimed subject matter of the application lacks technical advancement and is obvious in view of what was already known in the field at the priority date of the impugned application. Hence, in view of the disclosure of aforesaid prior art documents the invention claimed in the impugned application is obvious to a person skilled in the art.

B. Under Section 25(1)(f):

That, as detailed under the grounds of lack of inventive step, the invention of the instant application is obvious in view of the disclosure of the prior art. Further, the invention of the application lacks any technical advancement with respect to the similar formulations which are already known in the art at the time of the invention.

That the applicant has failed to give comparative data in the specification as filed establishing the enhanced therapeutic efficacy of the solid dispersion claimed in the application over solid dispersion formulation already known in art at the time of invention.

That a person skilled in the art knows that a solid dispersion of a drug is akin to a API which is then used to form a suitable pharmaceutical composition. That the solid dispersion of (R)-

1(2,2- difluorobenzo[D][1,3]dioxol-5-yl)-N-(1-(2,3-dihyderoxypropyl)-6- fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5- yl)cyclopropane carboxamide was already disclosed in US2009/131492 before the priority date of the impugned application. The applicant has not given any comparative data in the specification as filed establishing enhanced therapeutic efficacy of the solid dispersion claimed in present invention as compared to the solid dispersion known in US2009/131492.

Under Section 25(1)(g) :

That, the complete specification failed to describe in details the ratio /proportion of the components of the claimed solid dispersion. In absence, of these essential features a person skilled in the art has to undergo undue experimentation to arrive at the invention. Thus, due to lack of proper enablement and best mode of working in the specification a person skilled in the art has to exercise undue experimentation in order to arrive at the claimed invention. Therefore, the specification of the impugned application fails to sufficiently describe the invention.

Under Section 25(1)(h) :

The applicant has not filed the details of the prosecution of corresponding applications at the Patent Office and has, thus, failed to comply with the requirements of the provisions of Section 8 of the Act.

7. APPLICANTS 'S SUBMISSION:

The applicant although filed a reply in evidence against the grounds of the opposition but also filed an interlocutory petition. The main contention of the said interlocutory petition was based on the fact that the said pre-grant opposition was a benami opposition and thereby warrants the pre-grant opposition to be dismissed in limine.

Now in the reply in evidence the applicant filed the following-

A. Under Section 25(1)(d):

That the applicant agrees with the contents of Para 8 and 9 of the opposition that the compound (R)-1- (2,2-difluorobenzo[d][1,3]dioxol-5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2- methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (Compound 1), along with its method of preparation, is disclosed in the prior art document D1. However, the Compound 1 has been disclosed as one among more than 300 compounds disclosed in D1, all of which have been stated to be CFTR modulators. There is no teaching, suggestion, or motivation in D1 to a person skilled in the art to specifically select Compound 1 from the over 300 compounds disclosed in D1 that are also modulators of CFTR-mediated diseases such as CF.

B. That D1 discloses a solid dispersion comprising Compound 1 and a polymer, which may further comprise a surfactant. However, D1 generally teaches that the compounds disclosed therein may be incorporated into different types of formulations for administration, such as oral, liquid, and injectable. However, D1 does not disclose or suggest any formulation that might be orally bioavailable as well as stable, let alone a solid dispersion of Compound 1 comprising a polymer.

The technical problem with respect to the compound is poor solubility, consequent poor bioavailability, and instability of the amorphous form of Compound 1 in the solid state as well as the solution state. The invention provides a technical solution in the form of a formulation that leads to improved bioavailability and physical stability of the amorphous form of Compound 1 not only in the solid state but also in the solution state.

D1 discloses a list of various categories of pharmaceutical excipients that may be used to formulate the compounds of D1. However, D1 does not describe the claimed solid dispersion. There is no teaching provided in D1 as to which, if any, category of excipient that can be expected to give better bioavailability and stability of a particular form of the disclosed compounds. D1 is silent on the technical problem being addressed by the present invention. D1 does not suggest that any of the disclosed compounds, in the described forms, have any bioavailability issues, and so a person skilled in the art would not have considered that a specialized formulation was needed for any of the compounds disclosed in D1, let alone Compound 1, without hindsight knowledge of the claimed invention. D1 does not provide a person skilled in the art with a teaching or motivation to formulate a solid dispersion of substantially amorphous Compound 1 with HPMC or HPMCAS such that the drug remains in substantially amorphous form in the solid state as well as in the solution state.

That D2 discloses solid dispersion formulations of a single compound, the anticancer drug Tacrolimus. The inventors of D2 worked on the objective of forming various solid dispersions of Tacrolimus to enhance its solubility and bioavailability. D2 have neither assessed their solid dispersion formulation with other APIs nor professed anywhere in D2 that the same formulation may be applied to other APIs with an expectation of the same or similar results. The structure of the compound of the instant application and that of D2 is different. D2 has no way of predicting that the results of D2 will be emulated if Tacrolimus is replaced by some other API in the solid dispersion formulations disclosed in D2, such as Compound 1 of the instant application. Nor can the skilled person predict whether the enhancement in dissolution and bioavailability achieved by the use of polymers of D2 will be sufficient to achieve the desired therapeutic levels of another API. Hence, D2 does not provide a person skilled in the art with a teaching or motivation to use HPMC with Compound 1 of the instant application (or any compound other than Tacrolimus) in a solid dispersion, nor does D2 teach or suggest that such a solid dispersion will result in a similar stability and dissolution profile of Compound 1, similar to that observed in D2 for Tacrolimus. A person skilled in the art does not have a reasonable expectation of success that replacing Tacrolimus in the D2 formulation with Compound 1 will improve the physical stability and bioavailability of Compound 1.

That D3 pertains to formulating solid dispersions of a particular drug, AMG517, which shares no structural similarity with the compound 1 of the instant application. That disclosure of the polymers HPMC and HPMCAS in a prior art document for forming a solid dispersion teaches a person skilled in the art to use said polymers for forming the solid dispersion of Compound 1, and that the person skilled in the art would expect similar enhancement in stability and dissolution. D3 does not teach or suggest that the solid dispersion disclosed therein is applicable to Compound 1 of the instant application. D3 does not disclose or suggest that the physical and chemical properties displayed by the D3 solid dispersion are generally expected to be same for a solid dispersion comprising Compound 1 of the instant application and HPMC or HPMCAS. The disclosures of the prior art documents, considered alone or in combination, fail to teach,

suggest, or motivate a person skilled in the art to arrive at the present invention. The therapeutic efficacy of a drug can be dependent on the form of the solid, which is related to the physical stability of the solid. D1 discloses Compound 1 in amorphous form, and the instant application teaches that Compound 1 converts from amorphous form to crystalline form, which is less bioavailable. , the claimed solid dispersion displays an unexpected technical effect - improved physical stability and improved oral bioavailability over the neat amorphous Compound 1 disclosed in D1.

That formulation of a solid dispersion of Compound 1 is major development due its ability to resist crystallization and deliver a consistent dose of the amorphous drug substance. In particular, formulating amorphous Compound 1 with a polymer as a solid dispersion renders amorphous Compound 1 more physically stable and improves dissolution rates and bioavailability. This is based on data showing that solid dispersions of Compound 1 comprising either HPMC or HPMCAS were able to dissolve rapidly in aqueous conditions and, crucially, remain in solution for extended periods, in contrast with the neat amorphous Compound 1 as disclosed in D1. If Compound 1 is able to dissolve and, crucially, remain in solution for a long enough period in vivo, it will show a higher bioavailability than a form that crystallizes out of solution.

Under Section 25(1)(f) :

That the opponent has failed to establish any teaching, suggestion, or motivation for a person skilled in the art to arrive at the present invention based on the disclosure of cited prior art documents; and, the claimed solid dispersion comprising amorphous compound 1 is a technical advancement compared to the neat amorphous compound 1 disclosed in D1. It is also not clear from the opponents contention why a person skilled in the art would refer to the prior art documents, which are silent on the technical problem solved by the present invention Therefore, the present invention fulfils the requirements under section 2(1)(j) and does not fall under the bar of section 25(1)(f).

That the solid dispersion of compound 1 of the instant application was not available in the public domain . The opponent has not provided any prior art document that discloses a solid dispersion of Compound 1. Hence, providing comparative data in the specification of the formulation of the present invention against a non-existent formulation is unnecessary. A solid dispersion of the instant application is not required to be compared with a solid dispersion known in the art at the time of the invention, which does not contain the Compound 1. D1 does not disclose the solid dispersion of Compound 1. Hence, the notion of generating comparative data of a solid dispersion of the present invention with the imagined solid dispersion of D1 is completely inappropriate and unnecessary. The complete specification teaches that the therapeutic efficacy of a drug can be dependent on the form of the solid, and is related to the physical stability of the solid. D1 discloses compound 1 in amorphous form, whereas the instant application teaches that pure Compound 1 converts from amorphous form to crystalline form which is less bioavailable.

That a new formulation of compound 1 as a solid dispersion is developed which has the ability to resist crystallization and deliver a consistent dose of the amorphous drug substance. In particular, formulating amorphous Compound 1 with a polymer in a solid dispersion renders amorphous

compound 1 more physically stable and improves dissolution rates and bioavailability. This is based on data discussed in paragraphs 37 and 38 hereinabove, showing that solid dispersions of compound 1 comprising either HPMC or HPMCAS were able to dissolve rapidly in aqueous conditions and, crucially, remain in solution for extended periods, in contrast to the neat amorphous compound 1 disclosed in D1. Hence, the claimed solid dispersion comprising amorphous compound 1 possesses improved therapeutic efficacy compared to the neat amorphous compound 1 disclosed in D1.

That the claimed solid dispersion comprising amorphous compound 1 and a polymer renders amorphous compound 1 more physically stable and improves dissolution rates and bioavailability of compound 1 compared to the neat amorphous compound 1 disclosed in D1. Hence, the claimed subject matter does not fall under section 3(e) of the Act.

Under Section 25(1)(g) :

That the specification as filed discloses the percentages of the components of the solid dispersion and the composition in great detail, specifying the preferred, more preferred, and most preferred values for each of the components. Even the process parameters such as temperature and pH to be applied for arriving at the present invention have been elaborately detailed in the specification as filed. Hence, the complete specification of the instant application is sufficient and clear for a person skilled in the art to arrive at the claimed invention based on reading the specification as filed. Therefore, the complete specification fully and particularly describes the claimed invention to be performed by a person skilled in the art without performing undue experimentation.

Under Section 25(1)(h) :

That the details of the status of corresponding applications has been filed at the Patent Office, for example, on August 9, 2018, and June 4, 2019. Furthermore, for the instant application under the examination stage and, in any event, if the Controller seeks further information related to the search / examination of the corresponding foreign applications, the applicant will provide the same to the satisfaction of the Controller.

8. Pre-grant hearing :

The applicant and the opponent both were offered an opportunity of being heard through a pre-grant notice. No segregated hearing was proposed to be conducted in the said hearing notice. However, the opponent did not appear in the said pre-grant opposition and also did not make any submission with respect to their proposed attendance in the said hearing.

The applicant attended the scheduled hearing. However, it was surprisingly found that one of the representative of the applicant was also attending the hearing from abroad. Though the hearing under Section 25(1) is a public hearing, but as far as the attendance of the hearing of foreign nationals through video-conference are concerned, the same should be done as per prescribed norms. The appointed patent agents are supposed to take care of the same. Now, as a matter of settled principle of law, first the applicant was allowed to make their submissions with respect to the interlocutory petition they have submitted.

9. *The applicant mainly submitted the following with respect to their interlocutory petition. This was also submitted through their written submission which was followed by the hearing.*

   a. *That the present proceeding is nothing but a Benami Opposition and is clearly an abuse of the process of law, as the Opponent has no locus standi to file the present pre-grant opposition. The Opponent neither appeared for the hearing on the appointed date nor intimated the Controller that he will not be attending the hearing. That section 25(1) of the Indian Patents Act permits "any person" to file a pre-grant opposition against the granting of a patent. However, "any person" under Section 25(1) is not intended to create an individual right as such, but rather to provide access to any person to assist the Controller in taking a correct decision. The legislature has not conferred this right to be abused, therefore, the opponent cannot be a frontman. The right provided to "any person" to file a pre-grant opposition is not meant to abuse the process of law but to assist the Controller in deciding the outcome of a patent application. The applicant placed reliance on the order of the Hon'ble High Court of Mumbai in the matter of* *Dhaval Diyora v. Union of India & Ors, WP 3718/2020.*

   b. *The applicant also placed reliance on* *Pfizer Products Inc. v. Controller of Patents, IPAB, 2020, in OA/2/2016/PT/MUM,* *and* *Novartis AG v. Controller of Patents, IPAB, 2021 in OA/1/2021/PT/DEL.* *Citing the relevant paragraphs of the said mentioned orders, the applicant stressed that the opponent lacks bonafides and locus standi. Hence, the instant opposition is a Benami Opposition that was filed merely to delay the processes of law and patent granting.*

   c. *The applicant cited an internet investigation being carried out by themselves and pointed out that the opponent is employed as a managing partner at Sehgal IPR Services LLP, and have a dedicated official website. The applicant further provided the address of the opponent as available to them during this internet search operation being carried by them. The applicant further referred to an internet profile of the opponent being found in the public website named as LINKENDIN. The applicant further stressed on the information found by them by specifically referring to the fact that "Sehgal IPR Services is committed to providing top quality, comprehensive, responsive, and cost-effective intellectual property services to a diverse roster of domestic and international technology-based clients." Upon this self- investigation , the applicant also inferred to a decision by themselves that the nature of services provided by the IPR firm of the opponent clearly places the opponent in same shoes as a patent advisor/ lawyer and patent agent. The applicant stressed that the legislative intent under Section 25(1) was never to permit IPR firms, advocates or patent agents/ lawyers to step into the shoes of their client and file oppositions in their personal names Page 8 of 9 solely with a view to avoid revealing/ disclosing the names of the real parties (as front man).*

   d. *That the filing of the pre-grant opposition by a Managing partner of a IPR firm is nothing short of an abuse of the process of law, as the opponent has clearly not come to the Indian Patent Office with clean hands and is only a front man. The applicant placed reliance on the decision of a court in this regard and stated that the court has clearly cautioned against the rise of such oppositions and concluded that the "any person" language in Section 25(1) does not create individual rights. The applicant confirmed that they are unaware whether the opponent is a*

patent agent or not and therefore stands corrected with regard to paragraph 21 of the interlocutory petition.

e. *Additionally, the applicant also submitted that the present opposition is not warranted to be entertained as there are irrelevant references being cited by the opponent. This is also clear from the opposition statement and the prior arts cited as the opponent has not even understood or appreciated the invention that is directed to a solid dispersion of compound of formula 1. The prior arts cited are all irrelevant for the present invention for instance US 492 is for a new chemical entity for use as a CFTR modulator and discloses 300 compounds without any reference or teaching to the present invention relating to a solid dispersion. The other two references, Yamashita et and Kennedy et al are also not relevant as the said articles are in relation to compounds Tacrolimus and compound AMG517 respectively that are not even structurally, functionally or biologically similar to compound I let alone solid dispersion of compound I as claimed by the present invention.*

10. *The applicant was also offered a hearing under Section 14 of the Act with respect to the following objections-*

a. That Claims 1-20 are related to "A solid dispersion comprising substantially amorphous Compound I". The amorphous form is not allowable under section 3 (d) of the Act and accordingly, so-called solid dispersion is also not allowable.

b. Claims 11-20 are related to "A process of preparing a solid dispersion comprising substantially amorphous...." is beyond the scope of the originally disclosed claims. The said claims are also not allowable under section 3 (d) of the Act.

c. Claims 7-10 relating to so-called compositions are not allowable Section 3(d) of the Act, further the same also attracts Section 3(e) of the Act.

11. The applicant attended the said hearing. This was followed by a written submission along with an amended set of claims. The applicant mainly submitted as follows-

a. That the present invention is directed to a solid dispersion composition and is not attracted by Section 3(d) of the Indian Patents Act. The applicant placed reliance on the IPAB decision in the matter of 173/2013. That the patent specification teaches the therapeutic efficacy of a drug can be dependent on the form of the solid, which is related to the physical stability of the solid. D1 discloses Compound 1 in amorphous form, whereas the complete specification of the instant application teaches that pure Compound 1 converts from amorphous form to crystalline form, which is less bioavailable. The applicant has developed a new formulation of Compound 1 as a solid dispersion because of its ability to resist crystallization and deliver a consistent dose of the amorphous drug substance. Formulating amorphous Compound 1 with a polymer as a solid dispersion renders amorphous Compound 1 more physically stable and thereby improves the dissolution rates and bioavailability. Hence, solid dispersion of the instant application comprising amorphous Compound 1 possesses improved

therapeutic efficacy compared to the pure, unformulated amorphous Compound 1 as disclosed in D1.

b. That any drug which is not in solution does not get absorbed when the drug enters the intestinal tract, such as a crystalline drug. If Compound 1 is able to dissolve and, crucially, remain in solution for a long enough period in vivo as the thermodynamically unstable amorphous form quickly transitioned to a more physically stable but poorly soluble crystalline form. As the absorption of Compound 1 is solubility limited, the claimed solid dispersions of claim 1 would show improved bioavailability following oral administration. Hence, the claimed solid dispersions show an advantageous effect over the formulation disclosed in D1. The applicant referred to paragraph 12 of the patent specification that states that the properties of a solid relevant to its efficacy as a drug can be dependent on the form of the solid.

c. That the process claims relate to the process for preparing a solid dispersion composition as claimed in claims 1 to 10. Further, the said claims are not beyond the scope of the originally filed claims. The applicant placed reliance on order on the Hon'ble Delhi High Court in the matter of F. Hoffmann-La Roche Ltd. & Anr. vs. CIPLA Ltd., which referred to the principles of claim construction. The applicant also submitted a tabular format stating therein that claims 11-20 were derived from the original PCT claims and thereby they are not beyond the scope of the originally filed claims.

ANALYSIS AND FINDINGS :

The fresh amended claims as proposed by the applicant after the hearing under Section 14 are as follows-

1. A solid dispersion comprising substantially amorphous (R)-1-(2,2-difluorobenzo[d][1,3]dioxol5-yl)-N-(1-(2,3-dihydroxypropyl)-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl)cyclopropanecarboxamide (Compound 1) and a polymer selected from hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS), wherein the solid substantially amorphous Compound 1 comprises less than 15% crystalline Compound 1.

2. The solid dispersion as claimed in claim 1, wherein the polymer is present in an amount from 10% by weight to 80% by weight.

3. The solid dispersion as claimed in claim 1 or 2, wherein the solid substantially amorphous Compound 1 is present in an amount from 10% by weight to 80% by weight.

4. The solid dispersion as claimed in any one of claims 1 to 3, wherein the polymer is hydroxypropyl methylcellulose (HPMC).

5. The solid dispersion as claimed in any one of claims 1 to 3, wherein the polymer is hydroxypropyl methylcellulose acetate succinate (HPMCAS).

6. The solid dispersion as claimed in any one of claims 1 to 5, wherein the polymer is present in the amount of 20% by weight and the solid substantially amorphous Compound 1 is present in the amount of 80% by weight.

7. A process for preparing a solid dispersion composition as claimed in claim 1 comprising the solid substantially amorphous Compound 1 and a suitable solvent and then spray drying the mixture to obtain the solid dispersion.

8. The process as claimed in claim 7, comprising combining the solid substantially amorphous Compound 1 and a suitable solvent and then spray drying the mixture to obtain the solid dispersion.

9. The process as claimed in claim 8, wherein the solvent is an alcohol.

10. The process as claimed in claim 8 or 9, wherein the solvent is methanol.

11. The process as claimed in any one of claims 7 to 10, comprising:

a) forming a mixture comprising solid substantially amorphous Compound 1, a polymer, and a solvent; and b) spray drying the mixture to form a solid dispersion.

12. The process as claimed in claim 11, wherein the polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

13. The process as claimed in claim 11 or 12, wherein the polymer is present in an amount from 10% by weight to 80% by weight of the solid dispersion.

14. The process as claimed in any one of claims 11 to 13, wherein the solid substantially amorphous Compound 1 is present in an amount from 10% by weight to 80% by weight of the solid dispersion.

15. The process as claimed in any one of claims 11 to 14, wherein the solvent is methanol.

16. The process as claimed in any one of claims 11 to 15, wherein the solid substantially amorphous Compound 1 is present in the amount of 80% by weight of the solid dispersion, the polymer is HPMC and is present in the amount of 20% by weight of the solid dispersion, and the solvent is methanol.

Now as far as the pre-grant opposition is concerned, the primary thing which is to be considered and decided with respect to the allegation of the applicant is whether the said pre-grant opposition is a valid opposition as far as its viability is considered, and whether the said opposition is a benami opposition.

The opposition mainly relied on the fact that the opponent is an owner/managing partner of an IPR firm. Hence, the filing of a pre-grant opposition by the same is an abuse of the process of law. Some internet documents are relied upon by the applicant in this regard with respect to the professional profile of the opponent. None of the evidences (with respect to professional profile of opponent) are filed in the form of an affidavit.

The applicant's submission that the instant opposition procedure is not a public interest litigation and the opponent violated the provisions of the Indian Patents Act and Rules as his role ought to have been to uphold the integrity of the system and not abuse the law by filing oppositions in his personal name as partner of an IPR firm cannot be a matter to be decided by this tribunal. However, it has been observed that the opponent filed the pre-grant opposition in his name and through a registered patent agent. The opponent took specific grounds with respect to the filing of the opposition and in the reply of evidence the applicant also submitted point wise rebuttal for the same. However, upon fixation of pre-grant hearing, the opponent did not participate in the hearing. Neither, any communication was made to the Controller with respect to opponent's purported attendance for the scheduled pre-grant opposition hearing. It is also a fact on record that the

opponent did not made any submission with respect to the interlocutory petition as being filed by the applicant. The absolute silence by the opponent with respect to the allegations made by the opponent on different counts makes the applicant's contention stronger in nature but not convincing.

The applicant relied on the judgement of the Hon'ble Mumbai High Court wherein some specific observations were being made by the division bench against the allowability of the writ made by a serial pre-grant opposition filer against a tribunal refusal. Here the opponent could not be established as a serial habitual frontman as such, as no such evidence is being submitted by the applicant. But again, the non-attendance or non-communication of the opponents with respect to the attendance of the hearing makes the balance in favour of the applicant. The applicant or opponent is the best person to counter this argument.

Further, the non-attendance of the hearing by the opponent makes the balance in favour of the applicant. The pre-grant opposition as such cannot be taken on record in absence of the opponent in the hearing procedure. The pre-grant opposition is not a mere filing procedure. With the several judgements of the Hon'ble High Courts, the opportunity of hearing to the opponent has become mandatory in nature, which was duly offered to the opponent for the instant application. Again, at present the decision of Section 25(1) is also appealable in nature. Hence, as despite giving all opportunities the opponent did not appear in the scheduled hearing, neither filed any request for adjournment, the pre-grant opposition is hereby dismissed.

As far as the Section 14 hearing is concerned,, the applicant duly attended the said hearing and made their submissions. This was followed by a written submission along with an amended set of claims containing 16 claims.

Now, the following are disclosed by the applicant in their complete specification-

Page-1

The present invention relates to solid state forms, for example, crystalline and amorphous forms, of (R)-l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-N-(l-(2,3-dihydroxypropyl)- 6-fluoro-2-(l-hydroxy-2-methylpropan-2-yl)-lH-indol-5-yl)cyclopropanecarboxamide, pharmaceutical compositions thereof, and methods therewith.

Page -5

(R)-l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-N-(l-(2,3-dihydroxypropyl)-6- fluoro-2-(l -hydroxy-2-methylpropan-2-yl)-lH-indol-5-yl)cyclopropanecarboxamide is disclosed in US published patent application US20090131492 (said publication being incorporated herein by reference in its entirety) as a modulator of CFTR activity and thus useful in treating CFTR-mediated diseases such as cystic fibrosis. However, there is a need for stable solid forms of said compound that can be used readily in pharmaceutical compositions suitable for use as therapeutics.

Compound 1 and pharmaceutically acceptable compositions thereof are useful for treating or lessening the severity of CFTR mediated diseases such as, for example, cystic fibrosis. In one aspect, Compound 1 is in a substantially crystalline and salt free form referred to as Form A as described and characterized herein. In another aspect, Compound 1 is in an amorphous form as described and characterized herein. The properties of a solid relevant to its efficacy as a drug can be dependent on the form of the solid. For example, in a drug substance, variation in the solid form can lead to differences in properties such as melting point, dissolution rate, oral absorption, bioavailability, toxicology results and even clinical trial results.

Page-9-10

[0045] As used herein, a "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g. 9 colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include a crystalline drug (dispersed phase) in an amorphous polymer (continuous phase), or alternatively, an amorphous drug (dispersed phase) in an amorphous polymer (continuous phase). In some embodiments an amorphous solid dispersion includes the polymer constituting the dispersed phase, and the drug constitutes the continuous phase. In some embodiments, the dispersion includes amorphous Compound 1 or substantially amorphous Compound 1.

Page-10

[0046] The term "solid amorphous dispersion" generally refers to a solid dispersion of two or more components, usually a drug and polymer, but possibly containing other components such as surfactants or other pharmaceutical excipients, where Compound 1 is amorphous or substantially amorphous (e.g., substantially free of crystalline Compound 1), and the physical stability and/or dissolution and/or solubility of the amorphous drug is enhanced by the other components.

Page-15

[0070] In another aspect, the invention features a pharmaceutical composition comprising the solid dispersion and a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical composition further comprises an additional therapeutic agent. In another embodiment, the additional therapeutic agent is selected from a mucolytic agent, bronchodialator, an anti-biotic, an anti-infective agent, an anti-inflammatory agent, a CFTR potentiator, or a nutritional agent.

The applicant's main contention is that the instant application refers to a solid dispersion composition and thereby doesn't warrant the attraction of Section 3(d). Applicant stressed that D1 discloses Compound 1 in amorphous form, whereas the complete specification of the instant application teaches that pure Compound 1 converts from amorphous form to crystalline form. A new formulation of Compound 1 as a solid dispersion is developed by them because of its ability to resist crystallization and deliver a consistent dose of the amorphous drug substance. Formulating amorphous Compound 1 with a polymer as a solid dispersion renders amorphous Compound 1 more physically stable and thereby improves the dissolution rates and bioavailability. Hence, solid dispersion of the instant application comprising amorphous Compound 1 possesses improved therapeutic efficacy compared to the pure, unformulated amorphous Compound 1 as disclosed in D1.

Again, the admitted position of the applicant in their complete specification is that the compound -(R)-l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-N-(l-(2,3-dihydroxypropyl)-6- fluoro-2-(l -hydroxy-2-methylpropan-2-yl)-lH-indol-5-yl)cyclopropanecarboxamide is already known from the US published patent application US20090131492.

With respect to applicant's own admission and disclosure the document D1 is on record in the complete specification. The applicant's stressed on the fact that they have a dispersion to be claimed. But the dispersion is consisting of the compound already in public domain. The applicant further stressed that the

compound 1 is having both the forms in terms of crystalline and amorphous form. The applicant also indicated the role of some polymers as solid dispersion which is being in operation in the dispersion towards rendering the amorphous compound 1 as physically more stable and thereby increasing the dissolution rates and bioavailability. Though bio-availability cannot be considered as one of the factors towards consideration of therapeutic efficacy, but even the consideration requires some data which are totally missing from the complete specification as well in the applicant's further submission in terms of any affidavit. The applicant repeatedly stressed that the new formulation of Compound 1 as a solid dispersion is developed by them because of its ability to resist crystallization and deliver a consistent dose of the amorphous drug substance.

A simple search among the examples as cited by the applicant in their own complete specification does suggests any confirmatory message towards finding a single embodiment which proves the statement of the applicant that the dispersion results in improved therapeutic efficacy. Further there is no experimental data to prove the role of the polymers towards proving the statement of the applicant that the polymers are in a position to resist crystallization and thereby increase the percentage of the amorphous forms. In absence of data such claims can only be considered as a mere statement.

The abstract of the document D1 states as follows-

> Compounds of the present invention and pharmaceutically acceptable compositions thereof, are useful as modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator ("CFTR"). The present invention also relates to methods of treating ABC transporter mediated diseases using compounds of the present invention.

Section 3(d) of the Indian Patents Act (as amended) which bars inventions from patentability under the domain of non-patentable inventions stipulates as follows-

> the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.
>
> Explanation. -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;

In general chemistry -, dispersion is defined as a mixture whereby fine particles of one substance are scattered all through another substance.

Hence in absence of specific data, the application fails to establish the therapeutic efficacy of the compound being already known in domain of the art in particular form even being dispersed in another compound as dispersed medium wherein the compound retains its own identity as per the disclosure and submissions made for the instant application. The simple presence of the polymer in a particular phase fails to establish the fact that it should be considered as a combination as emphasised by the applicant citing a particular IPAB decision. It is pertinent to note that for the instant application the present claims refer to a dispersion and not a composition as such. In the instant case the applicant fails to establish with data the therapeutic efficacy of the particular form as being claimed by them. The stress on the fact that the polymers are only able to prevent the conversion of the particular amorphous form being converted into the crystalline form also confirms the fact about the sole action of the compound towards acting as a modulator of CFTR activity

and thus being useful in treating CFTR-mediated diseases such as cystic fibrosis. Hence the claims of the instant application fail to pass the Section 3(d) of the Act.

Again there were a total 80 claims in the PCT application which entered the national phase. Out of this 80 claims 1-20 referred to Form A of the compound, claims 21-23 referred to pharmaceutical composition, claims 24-32 relates to the process of preparing Form-A, claim 33-34 referred to solid amorphous form of compound, claims 35-37 to pharmaceutical composition of amorphous form, claims 38-39 referred to process of preparing amorphous form, claims 40-53 referred to the solid dispersion of amorphous form, claims 54-56 referred to a pharmaceutical composition of the solid dispersion, claims 57-60 referred to process of preparing the amorphous form, claims 71-79 referred to method of treatment, and, claim 80 referred to a kit. The claim 61 was as follows-

> 61. The process of any one of claims 57 to 60, comprising: a) forming a mixture comprising (i?)-l-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-N-(l- (2,3-dihydroxypropyl)-6-fluoro-2-(l-hydroxy-2-methylpropan-2-yl)-lH-indol5-yl)cyclopropanecarboxamide, a polymer, and a solvent; and b) spray drying the mixture to form a solid dispersion.

Hence claim 61 does not have a separate independent existence as a process for preparing dispersion. It was the subsidiary step in the process of preparation of the amorphous form of compound 1. So the examiner is correct in interpreting the fact that the present claims of process of preparation of dispersion is beyond the scope of claims as originally disclosed. Even if a benefit of doubt is awarded in favour of the applicant towards the formation of the dispersion through the subsidiary process of claim 61 still the proposed process claims towards formation of the dispersion as proposed could not satisfy section 3(d) of the Act.

From the general knowledge of chemistry dispersion is a mechanism in which, in a continuous phase of another substance, scattered particles of one material are dispersed. For the instant application the compound is known and the amorphous or crystalline Form A of the compound is considered as the same compound of the known compound. Hence the claims related to the process are also considered as a mere use of known process using known components.

Accordingly, the objections as raised in the hearing notice are accepted and it is found that subject matter of the claims of the instant application fails to pass the section 3(d) of the Act.

12. Now, on the above foregoing discussion, considering all facts and submissions made by both the applicant and the opponent, the pre-grant opposition filed under Section 25(1) of the Act against the instant application is hereby dismissed.

13. On the above foregoing discussions, considering all facts and submissions made by the applicant under Section 15 of the Act, the instant application is hereby refused for grant of patent.

(S.KUNDU)
Deputy Controller of Patents & Designs.

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