The Patent Act 1970

Section (15)

In the matter of the application for
Patent No. 9527 /delnp/2007 filed on 10th Dec,2007

M/s Gilad Science Incorporation ……..Applicant

Hearing held on Feb. 24,2011

Present:-

1. Mr. Natrajan **Agent for the applicant**
2. Dr. Rajendra Lohia **Examiner of Patents & Designs**

DECISION

An application for Patent was filed by M/s Natrajan & Subramaniam on December 10,2007 on behalf of the applicant M/s Gilad Science Inc. for an invention title " A method for forming a granular composition. "

This application was nationalized in India from international application no. PCT/US 2006/023222 dated June 13, 2006 published as WO 2006/135932 claiming priority of the corresponding application in the US being No. 60/610,010 dated June 13, 2005 and 60/771353 dated Feb 07, 2006.

FER issued on Oct. 10, 2010 with objections including the objection on novelty, Inventive step & industrial applicability under section 21(1)(j) with respect to the cited document WO 2004/64845, US 6645961 and Scientific discussion (Truvada) European medicines agency EMEA online Feb.25 etc.

The applicant submitted their reply along with supporting document and submitted that the prior art disclosed in the cited document teaches wet

granulated excepient and Tenofovir. These document also teaches that such composition becomes unstable when attempts are made to reduce the amount of excepient their in. The problem in the art was therefore providing a stable composition comprising a high proportion of emtricitabine and Tenofovir. Retaining these composition of the art and combining it with efavirenz would have made excepient load too high which would be too big to be conveniently taken by a patient. Also the stability of low excepient wet granulated formulation is believed to be the result of emtricitabine and tenofovir. Scientific discussion Truvada online , Feb. 2005 does not suggest dry granulation since it does not teach even that efavirenz has any stability that would required dry granulation. This citation actually teaches away from the present invention even assuming one knew about the problem of new eutectic mixture of TDS & FTL. For the above reasons it is submitted that the invention of the present application is inventive & non obvious over the cited prior art.

As the submission given by the agent to the applicant was not satisfactory w.r.t the invention ,a hearing was fixed on 24th Feb. 2011. In the written argument applicant submitted that the document WO 2004/64865 teaches the use of wet granulation to make a co-formulations of emtricitabine and tenofovir diisoproxil fumarates and also teaches that the composition are chemically stable. That mean the person skilled in the art would not look to further modify either the formulation itself or ever the method taught in WO 2004/64865. This citation does not teach the need or desirability of reducing the excepient load in the formulation. The problem was clarified for the first time by the applicants. The applicant tried to take the formulation of the WO/64865 and attempted to combine it with efavirenz and found the combined excepient and active load resulted in a tablet that was simply too large for a patient to swallow. This problem was never identified in any cited prior art. The applicant tried to reduce the size by reducing the carrier and excepient used in the TDF & FTL portion of the three component co-formulation but it was found unstable.

The reason considered by the applicant to be …. Melting of the crystalline API's during manufacture . This problem was identified in the present

application. The prior art does not teach or suggest this could be a problem in the manufacture of the formulation except one suggestion that one should stay with 1:1 mixture of TDF & FTL for stability in wet granulation formulation.

Again in US65645961 teaches dry granulation only because the drug indinavir sulfate is moisture sensitive and therefore dry granulation is actually used to reduce the amount of active ingredients.

In the EMEA report the problem was that when applicant tried to make the combination of three actives TDF, FTC & EPIV , the sum total of excepient and actives resulted in a tablet becoming to large to swallow by the patient and in the attempt to reduce the tablet size resulted in eutectic melting of the crystalline active during manufacture.

Therefore (1) dry granulation was not required since wet granulation gave the product required stability (WO 2001/64865) (II) even person by ordinary skill were to consider use of dry granulation it would be not preferred (being expensive, required equipment labour) & (11I) dry granulation even used would be actually to reduce the amount of active (US'961) The applicant pleaded that the objection of lack of inventive step be waived and the application be allowed for grant.

Order

The present application relates to a process for a combination product for treatment of HIV infection . The applicant in line 15 page 1 has acknowledged prior art WO 04/64845 which is assigned to the applicant itself which discloses chemically stable doses form of tenofovir disoproxil fumarate and emtricitabine produced by wet granulation (Truvada) is a chemically stable dosage form but does not contain efavirenz. Also HIV therapy using efavirenz as well as emtricitabine and tenofovir DF as a triple combination, disclosed in W004/64845 has been considered . (Page 1-3).

Therefore the object of the alleged inventors lies in the over coming the difficulties that one will come across in the course of manufacture of a dosage form that is a combination of tenofovir DF, emtricitabine and efavirenz. As explained on page 3 and 5 , additional obstacle to the triple combination dosage

form was that " combining the excepient present in the known commercial products Truvada and Sustiva tabltes was undesirable because the resulting tablet would contain the entire excepient load of the known tablets and thus would be large for a single tablet and present a dose from that was difficult to swallow and therefore inconvenient for the patient's use". It was thus an objective to prepare a highly concentrated proportion of emitricilabine and lenofovir DF which by reducing the amount of excepient in the preparation would contribute to an overall reduction in the size of the triple combination tablet. Page 3, line 19 of the prior art report successful manufacture of chemically stable truvada preparation by wet granulation but this was not feasible when the ratio of excepient to API is reduced to a managable amount for a triple combination tablet dosage form result in a chemically unstable preparation.

On page 5 line 4, ……"*In accordance with the invention a stable preparation of entricitabine /tenofovir DF is provided by dry granulating a composition comprising a pharmaceutical acceptable excepient, lenofovir DF and entricilabine. The omission of destabilizing amounts of water from the granulation process eliminates the disadvantageous formation of an emtricilabine /tenofovir DF eutectic mixture and enhances the stability of the resulting pharmaceutical products. The practice of the method of this invention produces a composition comprising dry granulated entricitabine and tenofovir DF".*

Therefore the claims are directed towards a method of preparing a two composents dry granulated composition. It is clear that the claim of the application do not conform with the object of the invention as is found on page 3 of the specification while the invention seeks to provide triple combination the method of claim 1 essentially provide a double combination .

"The same is evident from line 28 for page 10 that "It will be understood, however that the emtricitabine and tenofovir DF component of the tablet, which is an embodiment of the invention, optionally is manufactured for example as a stand alone product which is dry granulated tenofovir and emtricitabine" which is claimed in claim 1 is in total deviation from the object of the invention.

The dry granulation is a well known pharmaceutical manufacturing process and it is also admitted by the applicant vide line 15 page 5 of the US Patent No. 6645961, published on November 11, 2003, teaches a dry granulation formulation for HIV protease inhibitor. It provides "*in particular wet granulation is one of the more prevalent method for preparing tablets and/ or capsules. When tablet (Capsules) ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying and when tablets (Capsules) ingredients have sufficient binding or cohesive properties, slugging may be used to form granules. This method is also known a dry granulation. (Col 1, line 17-25)*. Therefore it is clear from the above teaching that in certain cases where the condition employed for the wet granulation are infavourable for the active to be granulated a person skilled in the art may alternatively switch to the technique of dry granulation.

On page 19 of the specification mention about the process of dry granulation followed for emtricitabine tenofovir DF , wherein emitricitabine, ….. cellulose, tenofovir DF and croscarmellose were blended in a blender for 10 minutes. Magnesium stearate was added , blended for five minutes and then transferred to a roller compactor. The granulation then were blended with croscasrmellose sodium and magnesium stearate. .

The cited document US 6645961 vide column 3 line 32- 45 provides , "More particularly illustrating the invention in the process comprising the step of (a) mixing about 76% by weight of indinavir sulfate with about 23% by weight anhydrous lactose and about 0.5% of magnesium stearate (b) compacting the mix from step (a) in a roller compactor (e) melting the component from the step (b) to from granules (d) lubricating the granule from step (e) with about 0.5% by weight of magnesium stearate and encapsulating ……" Compacting using roller compactor is well known in the art as is evident from the cited document US/65645961 employing known and standard step that form part of a dry granulation. The applicant is merely applying a well known industrial technique of dry granulation and therefore the

claim 1 and subsequent claims dependent upon it , uses a well known industrial technique.

On the page 21 of the cited document US WO 2004 064845, the excepients for tableting the ingredients are mentioned theirin -

------"*Tablet containing the active ingredients in admixture with non-toxic pharmaceutically acceptable excepients which are suitable for manufacture of capsules are acceptable. These excepients may be for example inert diluents such as calcium & sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, providone , calcium and sodium phosphate granulating and disintegrating agent such as maize starch or alginic acid binding agent such a cellulose microcrystalline cellulose , starch , gelatin or acacia and lubricating agent such as magnesium stearate steric acid or talc."*

The excepient shown above in the prior art are also the excepient used for emtricitabine /tenofovir DF combination mentioned on page 13 table 2.

Document cited is WO 2004 64845 published Aug 2004 relates to a chemical stable combination structurally diverse antiviral agent wherein vide page 3 line 8 provides that composition of tenofovir diisoproxil fumerate and emtricitabine are chemically stable and are either synergistic and/ or reduces side effect of one or both tenofovir DF and emtricitabine. Again on page 4 line 10 it teaches a chemically stable combination of tenofovir diisoproxil fumarate & emtricitabine. The same document on line 7 page 4 emphasizes " The unit dose form may be formulated for administration by oral or other routes and is unexpectedly chemically stable in view of the properties of the structurally diverse components."

Therefore from the above two paragraphs it is clear that the chemically stable formulation of TDF and emtricitabine existed in prior art much before the priority date of the present application.

The European Medicine Agency-scientific discussion, Truvada, EMEA (on line)February ,2005 vide page 1-28,relates to a fixed dose combination containing 200mg of emtricitabine and 300mg of tenofovir diisoproxil fumarate under heading 'composition' gives the ingredients of the formulation like croscarmellose sodium, magnesium stearate , microcrystalline cellulose and other

ingredients and these are the same ingredients used in the present application. Further on page 3 Para 5 states that emtricitabine and tenofovir diisoproxil fumerate are susceptible to hydrolysis in aqueous solution and to smaller extent degrade in high moisture /temperature condition with possibility of incompatibility between the two actives and its dissociated products. The discussion paper further submit *"a wet granulation has been chosen over the dry granulation in order to minimize the effect of physiochemical properties of the active substances on processing and blend uniformity. Control of the amount of the unbound water during manufacture and the finished product enhanced to minimize any potential degradation."*

On page 7, under heading 'stability of the product, states that stability data supports proposed self life and storage condition given in the summary of the product characteristics. "Given the physiological properties of the active ingredients and stability data result, wet granulated tenofovir/emtricitabine, is a chemically stable formulation, a fact that has been acknowledged by the applicant itself. However the same wet granulated TDF plus emtricitabine is used to formulate a triple combination product containing efavirenz, it does not result in a chemically stable formulation, another fact that has been acknowledged by the applicant on page 1, line 27-29. Hence a close reading of the specification will clearly bring to light that a dry granulated composition of tenofovir DF and emtricitabine is desired for the sole reason to make the same compatible in a triple combination formulation of these active with efivirenz. The claim in the application are merely a part of sequence of step that need to be followed to prepare a triple combination of TDF,emtricitabine and efivirenz.

Therefore following points are clearly indicated from the above analysis

(i) The wet granulation formulation of TDF and emtricitabine are known in the art and the formulation is **chemically stable** and acknowledged by the applicant also.

(ii)Dry granulation formulations are known in the art vide prior art US'961 .The applicant is merely applying a well known industrial technique of dry granulation and therefore the claim 1 which claims a method of dry granulation is obvious technique of preparation.

(iii) The pharmaceutical acceptable excepients used in the prior art are also the excepient used for emtricitabine and TDF combination mentioned on page 13 table 2 ,of the present application.

(iv) In the EMEA report (pub February,2005) the problem was that when a preparation of the combination of three actives TDF, FTC & EPIV were tried , the sum total of excepient and actives resulted in a tablet becoming too large to swallow by the patient and the attempt to reduce the tablet size resulted in eutectic melting of the crystalline active during manufacture.

(v)Again the European Medicine Agency-scientific discussion,Truvada,EMEA (on line)February ,2005 mentioned on page 4 that the physiological properties of the active ingredients and stability data results ,shows that wet granulation tenofovir/emtricitabine is a chemically stable formulation . However when the same granulated tenofovir/emtricitabine is used to formulate a triple combination product containing efavirenz, it does not result in a chemically stable formulation, clearly indicating that a dry granulated formulation of tenofovir / emtricitabine is desired for the sole reason to make the same compatible in a triple combination formulation of these with efavirenz.

(vi) Prior art US '961 provides that "*wet granulation is one of the more prevalent method for preparing tablets/capsules. When ingredients in the tablets/capsules are sensitive to moisture or unable to withstand elevated temperature during drying and when the tablets/capsules have sufficient inherent binding or cohesive properties, slugging may be used to form granules".*

(vii) There is no comparative study showing both dry and wet granulation method applied to the given composition in the specification of the application and therefore lacking in the justification of inventive step.

Therefore from the above analysis of these facts it is clear that the method for preparation of dry granulates of emtribilabine/ tenofovir DF produced by the method of claim 1 is obvious and totally devoid of any inventive merit in the light of the citations mentioned which suggested that, in certain cases where the condition employed for the wet granulation are unfavorable for the active to be

granulated ,a person skilled in the art may alternatively switch to the technique of dry granulation known in the art . Also claim 2 to 21 which are dependent upon claim 1 which claims the method of dry granulation of pharmaceutically acceptable excepients are also obvious & devoid of any inventive merit in the light of second citation i.e. WO 2004 664845 published Aug 5, 2004.

Claim 22 provides "*composition comprising greater than about 75%by weight of emtricitabine tenofovir DF and which contains less than about 15% by weight of eutectic mixture of emtricitabine and tenofovir DF* " The formation of eutectic mixture is solely attributed to the presence of water in the triple combination but none of the claims of the invention relates to triple combination of emtricitabine ,tenofovir DF and efavirenz. Therefore claim 22 is not supported by the description. Also the composition claim 22 lack in inventive step in absence of any comparative study data for dry and wet granulation method applied to the said composition.

On the basis of my above findings I am of the considered opinion that the claims are devoid of inventive merit and obvious with respect to the prior art and accordingly I refuse to proceed with the application for grant.

Dated 30th May,2011

(S .K.ROY)

Assistant Controller of Patents &Designs