THE PATENTS ACT, 1970
(39 of 1970)
as amended by
THE PATENTS (AMENDMENT) ACT, 2005
(15 of 2005)
(with effect from 1-1-2005)

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THE PATENTS RULES, 2003
as amended by
THE PATENTS (AMENDMENT) RULES, 2006
(with effect from 5-5-2006)

In the matter of Application for Patent bearing the number as 190/MAS/1998 filed on 29th January 1998 by F.HOFFMANN-LA ROCHE AG a Swiss Company of 124 Grenzacherstrasse, CH-4070 Basle Switzerland.

And

In the matter of Pre-grant Opposition by way of Representation under Section 25(1) of the Patents Act (as amended) by RANBAXY LABORATORIES LTD., an Indian Company of New Delhi.
HEARING HELD ON 31st MARCH 2006

In the presence of

Agents for the Applicant : Mr. D.J. SOLMAN of M/s DEPENNING & DEPENNING of Chennai.

Agent for First Petitioner : Mr. ANIL MISRA of LAKSHMI KUMARAN & SRIDHARAN of New Delhi.

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Assistant Controller of Patents & Designs : Mr. T.V. MADHUSUDHAN

Examiner of Patents & Designs : Mr. R. RAJINI

DECISION

M/s F. HOFFMANN-LA ROCHE AG a Swiss Company of 124 Grenzacherstrasse, CH-4070 Basle Switzerland, a Swiss Company, hereinafter referred as applicant for patent, have filed a convention application for patent for their invention titled ‘TETRAHYDROLIPSTATIN CONTAINING COMPOSITIONS’ on 29th day of January, 1998 through their agent M/s Depenning and Depenning of Chennai. The title of the invention was subsequently amended and the title of the invention reads as ‘A PHARMACEUTICAL COMPOSITION COMPRISING TETRAHYDROLIPSTATIN’. The applicant has claimed priority from two US applications viz., 60/037384 and 09/003137 dated 5th February 1997 and 6th January 1998 respectively for the invention titled ‘TETRAHYDROLIPSTATIN CONTAINING COMPOSITIONS’. The US application No. 09/003137 was granted in US on 21st December 1999 bearing the patent number 6004996. According to the statement given by the applicant under Section 8 of the Patents Act, the applicant had filed an International Patent Application on 24th January 1988 bearing the Application No. PCT/EP98/0039. It is further stated that out of 67 countries wherein the applicant has filed an application for patent for the substantially same invention, 57 countries have granted the Patent Right.
The applicant has filed a request for examination by filing Form 18 on 10th March 2005. The application for patent has been taken up for examination under the provisions of Section 12 of the Patents Act, 1970 and the First Examination Report [FER] was issued on 5th October 2005. According to the then Rules the Normal Period was due to expire on 5th April 2006. The applicant made a request on Form-4 for two-month extension of the normal period on 4th April 2006, which was subsequently granted by me. Therefore the Last Date to put the application in order was due to expire on 5th June 2006. Meanwhile the amendments for the Patents Rules were made effective from 5th May 2006 and according to new provision there is no Normal Period but only the Last Date is given to the applicant to put the application in order for grant. The Last Date is the end of the 12th month from the date of issue of FER. Therefore the last date in the instant application fell due on 5th October 2006. Neither knowing the intention of the applicant for making a request to extend the time limit nor the proposed amendments for the Patents Rules made effective from 5th May 2006 for putting the instant application in order for grant the hearing for pre-grant opposition was fixed on 31st March 2006 and was conducted on the scheduled date. The instant application was published under the provisions of Section 11(A) of the Patents Act, 1970 in the Patent Journal No. 07/2005 dated 4th March 2005.

Section 25(1) of the Patents Act stipulates that where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the grounds provided their under. M/s Ranbaxy Laboratories Limited, hereinafter referred as Opponent in this decision, through their attorneys M/s Lakshmi Kumaran & Sridharan have filed a Pre-grant opposition by way of a representation on 20th December 2005 on the following grounds namely;

i) The subject matter of the application stands anticipated
ii) The claimed invention lacks an inventive step
iii) The utility claimed is unsubstantiated
iv) No patent can be granted for a new form of a known substance
v) No patent can be granted for a composition, and
vi) The claims are indefinite.

In support of their arguments the opponent has filed 5 annexures as evidences, the details of which are;

i) US Patent 4598089, [‘089 patent]
ii) US Patent 5643874, [‘874 patent]
iii) Canadian Patent CA2128044 [a corresponding US Patent 5643874]
iv) Reynolds et al. [Manufacturing Chemist and Aerosol News, June 1970], and
v) Malinowski et al [Journal of Pharmaceutical Sciences, 1975]

Keeping the pre-grant opposition by way of representation aside I feel to disclose and discuss the invention as stated in the description, in terms of the problem identified with the prior art, solution offered by prior art and the technical solution as proposed;
PROBLEM IDENTIFIED

“THL, due to its low melting point of about 44 degree Celcius, undergoes both hydrolytic and thermal degradation, particularly when stored in a humid atmosphere or above 30 degree Celcius in a dry atmosphere. Furthermore, conventional dosage forms such as described in US Patent No. 4,598,089, for example, tablets or hard gelatin capsules, can not easily be formulated from powder mix or by conventional wet granulation procedure due to picking and sticking phenomena during tablet compression and encapsulation.” [Paragraph 2 of page 2 of the specification].

“Tetrahydrolipstatin has a low melting point. As a result, known formulations of tetrahydrolipstatin could not be used in conventional capsule-filling equipment to produce capsules containing 120 mg of tetrahydrolipstatin because the tetrahydrolipstatin within such formulations would melt during processing, resulting in the ‘picking and sticking phenomena’ as well as reduced chemical stability.” [Paragraph 5 of page 6 of the specification].

SOLUTION OFFERED BY PRIOR ART

“The conventional technique for addressing the picking and sticking phenomena in the capsule-filling equipment is to lower the processing temperature or to lower the concentration of the heat-sensitive substance in the formulation to be encapsulated.”

PROPOSED TECHNICAL SOLUTION

By controlling the particle size of the pellets, whose range is within 0.25 mm to 2.0 mm, the problem of picking and sticking phenomena is avoided thereby the capsules of 120 mg could be manufactured without facing the problems as faced in the prior art.

Paragraph 4 of page 3 of the specification is reproduced herein which is a proposed technical solution according to the applicant.

“Surprisingly, it was found that THL containing particles (also called multiple units) minimize the sticking and picking phenomena encountered during tablet compression or encapsulation. In one of its aspects, the present invention relates to a unit dosage form comprising a plurality of pellets having a diameter in the range of from 0.25 mm to 2.0 mm wherein each particle comprises tetrahydrolipstatin, a stabilizer and at least one pharmaceutically acceptable excipient. When the particles are in the form of pellets, it is critical to employ microcrystalline cellulose.”

Before proceeding further it is pertinent to reproduce the claims as filed.
1) A pharmaceutical composition comprising a plurality of particles having an average diameter of from about 0.25 mm to about 2 mm, each particle comprising tetrahydrolipstatin, a stabilizer, and at least one pharmaceutically acceptable excipients, provided that when the particles are in the form of pellets, each pellet contains microcrystalline cellulose.

2) The composition of claim 1, wherein the particles are pellets or granules, particularly wherein the pellets or granules have an average diameter of from about 0.5 mm to about 1.5 mm.

3) The composition of claim 2, wherein the stabilizer is selected from the group consisting of polyvinyl pyrrolidine, lactose, a combination of polyvinylpyrrolidone and lactose, hydroxypropyl methyl cellulose and hydroxy propyl cellulose.

4) The composition of claim 3, wherein at least 5% by weight of the composition is polyvinylpyrrolidone.

5) The composition of claim 3, wherein the stabilizer is a combination of lactose and polyvinylpyrrolidone wherein at least 3% by weight of the composition is polyvinylpyrrolidone.

6) The composition of claim 2, wherein the pharmaceutically acceptable excipients is a surfactant, diluent or disintegrant.

7) The composition of claim 6, wherein the pharmaceutically acceptable excipients is a surfactant, particularly wherein the surfactant is sodium lauryl sulfate or sodium dioctylsulfosuccinate.

8) The composition of claim 6, wherein the pharmaceutically acceptable excipients is a diluent, particularly wherein the diluent is microcrystalline cellulose, sucrose or starch.

9) The composition of claim 6, wherein the excipients is a disintegrant, particularly wherein the disintegrant is sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-carmolose sodium, or low-substituted hydroxy propyl cellulose.

10) The composition of claim 2 which comprises from about 20% to about 75% by weight of tetrahydrolipstatin; from about 3% to about 60% by weight of stabilizer; and from about 10% to about 60% by weight microcrystalline cellulose.

11) The composition of claim 10 which comprises about 25% to about 75% by weight tetrahydrolipstatin; from about 20% to about 60% by weight microcrystalline cellulose; from about 1% to about 10% by weight sodium starch glycolate; from about 1% to about 8% by weight sodium lauryl sulfate; from about 1% to about 10% by weight polyvinylpyrrolidone; and from about 0% to about 1% by weight talc.

12) The composition of claim 11 which comprises about 50% by weight tetrahydrolipstatin; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% by weight polyvinylpyrrolidone; and about 0.1% by weight talc.
13) The composition of any one of claims 1, 2 and 10-12 which is unit dosage form.

14) A pharmaceutical composition as in claim 1, which comprises about 120 mg of tetrahydrolipstatin; about 93.6 mg of microcrystalline cellulose; about 7.2 mg of sodium starch glycolate; about 7.2 mg of sodium lauryl sulfate; about 12 mg polyvinylpyrrolidone; and about 0.24 mg talc.

15) The composition of claim 14 which is in unit dosage form.

16) A pharmaceutical composition substantially as herein described and exemplified.

During the prosecution of the application various objections were raised and the applicant has promptly replied to all the queries raised. For the sake of brevity the details of correspondences between the applicant and the Patent office is not reproduced herewith but a synopsis of the entire action is briefly discussed herein. There were objections with respect to novelty, inventive step, non-allowability under Section 3(d), 3(e) and insufficiency of disclosure under section 10 of the Patents Act. While answering to the objections raised by Patent Office the applicant has submitted that the Novelty and Inventive step are not destroyed by the cited US patent 4598089 as the cited document does not disclose the technical feature of the present invention. It was stated that according to the present invention the pharmaceutical composition comprises particles of a certain defined size [0.25 to 2 mm] and that each individual particle must comprise all the components [tetrahydrolipstatin, a stabilizer, at least one excipients]. It was prayed that the alleged invention is not a mere admixture of the ingredients as stated but it is the composition of particles wherein each particle has all the ingredients as stated. It was further stated that the composition as claimed have the unexpected advantage that they can be easily formulated and do not exhibit picking and sticking phenomenon during tablet compression or encapsulation. The applicant stated that the present invention does not attract the provisions of Section 3(d) of the Patents Act as the present invention relates to a composition but not to a substance. It was argued by the applicant that the present disclosure neither attracts the provisions under Section 3(e) of the Patents Act, as the claimed pharmaceutical composition has a synergistic effect of increased thermal and hydrolytic stability and reduced sticking and picking phenomenon. To a specific query [under section 10 of the Patents Act], on how to obtain the particles having all the ingredients in the desired ratio as claimed in the specification and with respect to non-disclosure of a specified process wherein each particle of a specified size containing the ingredients in the ratio as claimed is obtainable, the applicant responded that there is no specific process but the process of obtaining the particles of the invention has been generally exemplified in examples 1 and 2 and it can be a conventional process also.

PROCEEDINGS OF PRE-GRANT OPPOSITION BY WAY OF REPRESENTATION

The photocopy of the representation of the opponent was forwarded to the agent of the applicant on 10th February 2006 and further communication on 3rd March 2006. Since both the opponent and the applicant have made a request for the personal appearance before me, a hearing was conducted on 31st March 2006.
During the hearing the agent for the opponent stated that that THL, the active ingredient is anticipated by ‘089 patent. The ‘089 patent further discloses the pharmaceutical compositions wherein the percentage composition of THL is same as disclosed in the present application for patent. It was further argued that with respect to other ingredients and as admitted by the applicant there is nothing new. It was further argued that the applicant has stated in his present application that the process of preparation is a known method to the person skilled in the art; use of microcrystalline cellulose is also anticipated. The ‘874 patent discloses a number of compositions which are similar to the compositions claimed in the present application. And therefore it was prayed that the instant application should be rejected.

In his further arguments the opponent’s agent was referring to Reynolds et al and Malinowski et al publications [1970 and 1975 respectively] wherein it is disclosed that the process of pelletization can be adopted to prepare pellets containing thermally liable materials with various particle sizes. Hence a person skilled in the art can come to a conclusion that the problem posed due to low thermal stability can be solved by pelletization thus the present invention lacks in inventive step. Therefore it was prayed to reject the present application.

On the utility, the agent for the opponent stated that the assertions of the present invention are completely unsubstantiated by any data and therefore the patent should be rejected.

It was pointed out by the opponent that the present invention could not have been filed under the then Section 5(2) because the application does not claim any clinical or pharmaceutical utility.

Referring to Section 25(1)(g) of the Patents Act the opponent states that the complete specification which does not sufficiently and clearly describe the invention or the method by which it is to be performed shall be rejected as the instant application for patent failed to fulfill this requirement. It was prayed by the opponent that the application is in contravention of section 10(5) and 25(1)(g) of the Act and is indefinite and no patent can therefore be granted.

Before ending the arguments the agent for the opponent further argued that the claims attracts the provisions under section 3(d) and 3(e) of the Patents Act as particle sizes of a substance if constitutes an invention is not patentable subject matter and therefore the application shall be rejected.

In response to the opponent’s objections the agent for the applicant has argued and stated that they deny all and singular allegations made therein and wish to submit that the invention is novel, non obvious, involve inventive ingenuity and overcomes certain disadvantages of the state of art prior to this invention.

The applicant agrees that THL is a known compound and they do not claim THL as such but the invention relates to compositions that contain THL as active ingredient. It was argued that the problems like chemical instability, sticking and picking phenomena were discussed at length in the description and how to solve the aforesaid problems was also discussed with the examples. The solution provided by the inventors in the present invention is plurality of particle with diameter of 0.25 mm to 2.0 mm, each particle comprising THL, stabilizer and pharmaceutically acceptable excipients.
With regard to ‘089 patent it was argued that the compositions disclosed in ‘089 patent comprises THL in the range of 6% to 95% with other pharmaceutically acceptable inert carrier material. The said US document does not disclose composition according to the present invention, which comprises THL, a stabilizer and pharmaceutically acceptable excipients in the form of pellets with diameters ranging from 0.25mm to 2.0 mm, wherein each individual particle comprises each of the three components. Thus the cited document does not destroy the novelty but the present invention is an improvement over the cited document. Therefore it was prayed that the opposition be dismissed and patent may be granted.

It was further argued that the ‘874 patent too does not disclose the particles of specific size and ingredients as claimed in the present application and therefore patent be granted to the applicants.

The agent for the applicant further stated that the opponent has failed to assess the inventive step on the grounds namely;

(i) that there is some teaching or suggestion in the cited prior art that would motivate the skilled artisan to modify the prior art;
(ii) some expectation that such modification would work

Reynolds et al document discloses a technique for the production of spherical particles but neither discloses the problem neither faced during tablet formation of orlistat nor suggests any formulation to overcome this problem. The cited document discloses only a general technique and this technique is extended to food, agriculture and other products apart from pharmaceuticals. The same argument is provided for the Journal Malinowski et al wherein the cited document teaches that for heat liable materials special measures must be taken but is does by no means that this could be preferred over other methods for compounds such as orlistat. Therefore it was prayed to grant the patent.

The agent for the applicant stated that the data on substantial utility has already been given in the specification.

In his presentation it was pointed out that the present invention relates to a composition of medical utility and therefore could have been filed under the then Section 5(2) of the Patents Act as the claimed composition is hitherto unknown and can be used as anti-obesity agent.

It was prayed and argued that the specification has satisfied the requirements of Section 10(5) and the invention is substantiated with examples wherein specific ratios of the ingredients and the particle sizes have been provided, hence patent may be granted.

With respect to Section 3(d) of the Patents Act the applicant has argued that particle sizes as defined in Section 3(d) is to compounds but not for compositions. Further it is stated that the invented composition is not a new form of the active ingredient but it is a new composition. The present invention is not a mere admixture, it is plurality of particles wherein the particles have an average diameter ranging from 0.25mm to 2.0mm and each particle comprises THL, a stabilizer and a pharmaceutically acceptable
excipient. The composition of the invention has a synergistic effect of increased stability and reduced sticking and picking phenomena.

The applicant has submitted an affidavit signed by Mr. Navnit Hargovindas Shah on 31st day of March 2006 before a Notary Public in US, who is holding a senior position as Distinguished Research Leader in the Pharmaceutical Research and Development Department of Hoffmann-La Roche Inc. The affidavit comprises the same statement as provided by the agent of the applicant during the personal hearing and hence the contents of which is not discussed herewith.

Summing up the arguments the agent for the applicant has prayed that since the opponent has failed in his efforts and the applicant has proved the criteria like novelty, inventive step and industrial applicability the opposition shall be rejected and the applicant be granted a patent.

After completing the proceedings under section 25(1) and at the end of the prosecution of the application the applicant has submitted his final amendment of claims for the consideration of grant of a patent. The final set of claims is;

1. A pharmaceutical composition comprising a plurality of particles having an average diameter of from 0.25 mm to 2 mm, each particle comprising tetrahydrolipstatin, a stabilizer selected from the group consisting of polyvinylpyrrolidone, lactose, a combination of polyvinylpyrrolidone and lactose, hydroxypropylmethyl cellulose, and hydroxypropyl cellulose, and at least one pharmaceutically acceptable excipient wherein the pharmaceutically acceptable excipient is a surfactant, diluent, or disintegrant, provided that when the particles are in the form of pellets, each pellet contains microcrystalline cellulose.

2. The composition as claimed in claim 1, wherein the particles are pellets or granules, particularly wherein the pellets or granules have an average diameter of from 0.5 mm to 1.5 mm.

3. The composition as claimed in claim 3 wherein at least 5% by weight of the composition is polyvinylpyrrolidone.

4. The composition as claimed in claim 3 wherein the stabilizer is a combination of lactose and polyvinylpyrrolidone wherein at least 3% by weight of the composition is polyvinylpyrrolidone.

5. The composition as claimed in claim 1 wherein the pharmaceutically acceptable excipient is a surfactant, particularly wherein the surfactant is sodium lauryl sulfate or sodium dioctylsulfosuccinate.

6. The composition as claimed in claim 1 wherein the pharmaceutically acceptable excipient is a diluent, particularly wherein the diluent is microcrystalline cellulose, sucrose or corn starch.

7. The composition as claimed in claim 1 wherein the excipient is a disintegrant, particularly wherein the disintegrant is sodium starch glycolate, cross linked polyvinylpyrrolidone, cross carmolose sodium, or low substituted hydroxypropyl cellulose.
8. The composition as claimed in claim 2 which comprises from 20% to 75% by weight tetrahydrolipstatin; from 3% to 60% by weight stabilizer; and from 10% to 60% by weight microcrystalline cellulose.

9. The composition as claimed in claim 8 which comprises 25% to 75% by weight tetrahydrolipstatin; from 20% to 60% by weight of microcrystalline cellulose; from 1% to 10% by weight sodium starch glycolate; from 1% to 8% by weight sodium lauryl sulfate; from 1% to 10% by weight polyvinylpyrrolidone; and from 0% to 1% by weight talc.

10. The composition as claimed in claim 9 which comprises about 50% by weight tetrahydrolipstatin; about 39% by weight microcrystalline cellulose; about 3% by weight sodium starch glycolate; about 3% by weight sodium lauryl sulfate; about 5% by weight polyvinylpyrrolidone; and about 0.1% by weight talc.

11. The composition as claimed in claim 1 which comprises about 120 mg of tetrahydrolipstatin; about 93.6 mg of microcrystalline cellulose; about 7.2 mg of sodium starch glycolate; about 7.2 mg of sodium lauryl sulfate; about 12 mg polyvinylpyrrolidone; and about 0.24 mg talc.

12. The composition as claimed in any of claims 1, 2 and 8 to 10, which is in unit dosage form.

After giving a deep thought with respect to the proceeding under Section 25(1) of the Patents Act and the proceedings with respect to prosecution of the application I have come to the following conclusions;

The invention as stated by the applicant lies in the SIZE OF THE PARTICLE WHICH IS A COMPOSITION BY ITSELF. During the prosecution the agent of the applicant was explaining that the applicant is not claiming the composition but the size of the particles, which is having a diameter ranging from 0.25 mm to 2 mm wherein each particle is a composition by itself. In other words ONLY SIZE matters in the alleged invention BUT NOT THE COMPOSITION; as all the ingredients are known which was admitted by the applicant. The applicant was also explaining that the AVERAGE DIAMETER AS CLAIMED IS NOT THE AVERAGE DIAMETER OF TETRAHYDROLIPSTATIN BUT THAT OF A PARTICLE WHICH COMPRISES ALL THE INGREDIENTS VIZ., TETRAHYDROLIPSTATIN, A STABILIZER AND A PHARMACEUTICAL EXCIPIENT.

The next question arises in mind that what is a composition? Let me imagine a homogenous composition, which comprises tetrahydrolipstatin, a stabilizer and a pharmaceutical excipient as separate entities but homogenously mixed in the said composition. Let the pellets be prepared from this homogenous composition with a diameter ranging from 0.25 mm to 2.0 mm. Does each pellet contain the same homogenous composition or different composition? As far as the common sense goes to my understanding each pellet should comprise the same composition and the ingredients should be in the same ratio. Otherwise I should adopt a different process wherein I should be able to achieve the pellet and each pellet shall contain all the ingredients in predetermined ratio. As disclosed in the specification there is no special process provided to prepare the particles and pellets from such particles wherein each particle comprising all
the ingredients in the predetermined ratio. Besides the applicant has disclosed in page 5 of the specification that “THE PROCESS FOR PREPARING THE PELLETS IS KNOWN PER SE”, BUT NO WHERE IT IS MENTIONED HOW TO PREPARE A PARTICLE HAVING ALL THE INGREDIENTS IN A PRE-DETERMINED RATIO.

In the words of the applicant it is the size of the particle or a pellet, which overcomes the problems of chemical stability, picking and sticking phenomena. Comparative examples were provided in the specification with respect to picking and sticking phenomena wherein the results shown proves that the problem of picking and sticking phenomena has been overcome. No substantative explanation has been provided with respect to chemical stability that is achievable from the alleged invention.

The invention as disclosed passes the Novelty test but lacks in Inventive step. The disclosure of the invention also fails to comply with the requirements under Section 10 of the Patents Act, 1970.

Therefore the grant of patent is hereby refused. No costs are awarded.

Dated this 22nd day of January 2007.

(T.V.MADHUSUDHAN)
Assistant Controller of Patents and Designs.