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Research article

Retrospective and Analytical Study of the Doctrine Related Pharmaceutical Polymorphism and Patents

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Abstract

Called pharmaceutical polymorphism to change of the crystal structure of a substance when it is in its solid state, this has generated a controversy over whether or not to enjoy protection for patents for invention, and that it could limit or delay the access of generic drugs to health care centers, or services, this study aims to define the main technical characteristics of pharmaceutical polymorphs and determine its patentability under Costa Rican law, such legislation also compared with the doctrine poured into other countries, mainly the United States of America. Methodology: Written information sources and electronic media since 1850 to February 2014 were revised, data were collected and information was placed in an instrument that selects the main themes. Then it was analyzed by triangulation and conclusions were made by technical and legal criteria. Results: Among the main results the eligibility of patentable matter was determined against the non-patentable, the main technical criteria of pharmaceutical polymorphs for a prior art study were established and the differences between the US and Costa Rican law doctrine on the subject of polymorphism and patents was determined.

Key words: Drugs, Patents, Pharmacy, Pharmaceutical polymorphism, physicochemical properties.

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1. Introduction

A patent is a contract between the state and an applicant that grants certain exclusive rights mainly in the commercial sector for material that meets special requirements, in particular novelty, inventive level and industrial application, in exchange of that the beneficiary makes public the information on how to completely reproduce this protected material, which is meant to be in the domain and free use for the public, once the protection finalizes. This type of industrial property has as main purpose to promote innovation and common benefit, however, sometimes the private interest overcomes the public interest which generates

controversy involving mainly health issues, such as medications [1,2].

Called pharmaceutical polymorphism to the property of a solid to solidify into different three-dimensional shapes, this could include different crystalline forms as it is commonly understood the concept, but when the subject includes patents for invention also spoken of solvates, clathrates and amorphous [3].

The issue of polymorphism and patents has caused controversy mainly because some authors consider its patentability, as a block or delay to the introduction of generic drugs to the market, also other authors consider that patents of polymorphs can foster innovation in this field [4, 5, 6].

The definition of pharmaceutical polymorph must be extended in order to understand a little more the arguments that will be discussed on the subject of polymorphs and patents, should be established as this process occurs, a chemical with decreasing temperature allows the atoms to approach and reaches what is known as solid state where interactions between molecules and atoms are restricted due to the proximity between themselves, depending on the cooling rate and other characteristics of the nature of each substance features like elements and functional groups that form, solvent, impurities, among others, the chemical is arranged repetitively to this is known as a glass, or they are approaching without a repeating pattern this is called an amorphous, also can incorporate a molecule of solvent this is called a solvate [7, 8].

These different forms of solidification confer different physical properties such as melting point, the rate of dissolution, density, among others, however the chemical properties are not changed as the nature of the compound remains the same, i.e. functional groups or atomic elements remain unchanged but are arranged in different ways [9,10].

However, the pharmaceutical properties could be affected by changes in physical properties such as some substances, such as azithromycin or atorvastatin, may reduce its bioavailability by changes in the dissolution rate, however in many other occasions does not happen an affectation as is the case of Forms I and II of enalapril maleate [11,12].

The nomenclature classification of pharmaceutical polymorphs is often arbitrary, using Roman numerals as I, or II, Greek letters alpha, beta, or Arabic numerals 1, 2, in order of their discovery, although crystallographic level there is a systematic nomenclature for crystalline forms, usually reported in this patent descriptions, but are not useful to define amorphous substances or clathrates, and sometimes polymorphic purity is not always one hundred percent and this prevents completely determine the polymorph [11 12].

For the above reason, polymorphs in pharmaceutical patent invention documents are defined by their physical properties as melting point, Raman spectrum, X-ray diffraction, thermogram, IR spectrum, and others [11].

First, the present study aims to define the main technical characteristics of pharmaceutical polymorphs and determine its patentability under Costa Rican law, such legislation also compared with the doctrine poured into other countries, mainly the United States.

2. Materials and Methods

The present study is one of comparative-analytical retrospective nature, a search of the prior art documents on the Internet and databases was performed, as well as books and magazines, using criteria and words of arbitrary key defined by the

researcher, between keywords used are polymorphism, crystal, polymorph, amorphous, patent invention, patent, and combinations thereof.

Among the consulted sources are Scinfinder, Ebsco Host, PATENTSCOPE, Espacenet, Google, Yahoo, Google patents, Google Scholar, Database Library System of the University of Costa Rica SIBDI, Register Plus, Hinari.

The selection criteria used by the researcher were, in order of priority 1) specialized documents that combine the issue of pharmaceutical patents and polymorphism, 2) Documents on patent law (guidelines, guides, items), 3) Documents on pharmaceutical polymorphism, 4) Other relevant documents as historical documents, references, etc.

After the selection of documents and their classification, the main ideas are extracted and the technique of triangulation is used to relate the concepts and discourse analysis by comparing them, at the end the main conclusions found are systematically ordered.

3. Results and Discussion

In order to understand the patentability or non-patentability of pharmaceutical polymorphs, you must understand the concept of invention as indicated by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), and some major patent laws including the Costa Rican one, this comparison is shown in Table 1, very attached to the concept of invention, is the criterion of eligibility more characteristic of the American doctrine where states which matter is eligible for patent, table 1 also incorporates the concept of eligibility to show a more complete environment.

Table 1. Comparison of criteria of patentable subject matter (invention or eligible matter for patent in several countries or international organizations) [13,14,15,16,17,18,19,20].

Country or organization	Invention criteria or matter eligible for patenting
TRIPS (WTO)	ADPIC Article 27, paragraph 1. Subject to paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new and involve an activity inventive and capable of industrial application. [5]. Notwithstanding the provisions of paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights shall be enjoyable without discrimination as to the place of invention, the field of technology and whether the products are imported or locally produced. 2. Members may exclude from patentability inventions whose commercial exploitation within their territory must be prevented to protect public order or morality, including to protect the health or life of humans or animals or to preserve plants, or to avoid serious damage to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law. 3. Members may also exclude from patentability: a) Diagnostic, therapeutic and surgical methods for treating humans or animals; b) Plants and animals other than microorganisms, and essentially biological processes for the production of plants or animals other

	than non-biological and microbiological processes. However, Members shall provide for the protection of plant varieties either by patents or by an effective sui generis system or a combination of the two. The provisions of this subparagraph shall be reviewed four years after the entry into force of the WTO Agreement.
Costa Rica	Law # 6867 Article 1º.- Inventions. 1. Invention is any creation of the human intellect, capable of being applied in industry, meeting the conditions for patentability under this law. It may be a product, a machine, a tool or a manufacturing process and will be protected by the patent. 2. For the purposes of this law will not be considered inventions: a) Discoveries, scientific theories, mathematical methods and computer programs in isolation. b) Purely aesthetic creations, literary and artistic works. c) Plans, principles or economic methods of advertisements or business and those referring to purely mental, intellectual activities or to games. d) The juxtaposition of known inventions or mixtures of known products, variations in their form or use, dimensions or material, except in the case of a combination or merger such that they cannot function separately or that the qualities or functions of them are modified to obtain an industrial result not obvious to one skilled in the art.
United States of America (USPTO)	35 U.S,C § 101 -Inventions Patentable: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. 35 U.S,C § 101-invenciones patentables: Quienquiera que invente o descubra cualquier proceso, maquina, manufactura, o composición de materia novedosa y útil, o cualquier mejora novedosa y útil en aquellas, podrá obtener una patente sujeta a las siguientes condiciones y requerimientos de este titulo..
Cuba	Law 290 ARTICLE 21.1.-It is understood the invention capable of being protected by patent, any technical solution in any field of technology, possessing novelty, inventive step and industrial applicability. 2. An invention may only cover: a) Products; and b) Procedures. 3. Considered inventions: a) plans, rules and methods for performing mental, sporting, recreational, economic and commercial activities; b) the projects, schemes and drawings of buildings; c) Discoveries that consist in publicizing laws, phenomena or properties of the material universe; d) the existing material in nature, either bare or insulated, including biological and genetic, parts, chemicals and replicas, except for microorganisms defined in Section 4 of this article;

	e) The principles and scientific theories; f) Mathematical methods; g) Ways of presenting information; h) Layout designs of integrated circuits; i) Computer programs, scientific, artistic and literary and aesthetic creations; j) Essentially biological processes; k) The human body, at the various stages of its formation and development, the discovery of some of its elements or parts and replicas including sequences or partial sequence of a gene and its genetic identity, even if using a technical procedure for their production; l) The patented products or processes within the state of the art, for the simple fact to a different use covered by the original patent; m) Those that contradict the scientific principles and laws governing phenomena and properties established in science; n) The change in shape, size, proportions or material of an object unless it essentially modifies the properties of this. o) The juxtaposition of known inventions or mixtures of known products; alteration of the use, form, dimensions or materials, except in the case of combination or merger, so that the qualities or functions characteristic thereof are modified to obtain a new industrial result that cannot be derived from the separate application of the juxtaposed inventions; p) The use of products and procedures; and q) Products and applications based procedures.
European Union (EPO) European Patent Convention	European Patent Convention Article 52. Patentable Inventions 1. European patents shall be granted for any inventions in all fields of technology, provided that they are new, which involve an inventive step and is industrially applicable. 2. Not to be considered inventions for the purposes of paragraph 1, in particular: a) Discoveries, scientific theories and mathematical methods; b) Aesthetic creations; c) Schemes, rules and methods for performing mental acts, on games or in the field of economic activities, as well as computer programs; d) Presentations of information. 3. The provisions of paragraph 2 shall exclude patentability of the items referred to therein only to the extent that the European patent application or European patent relates to more than one of these elements considered as such.
Argentina	Law No. 24,481 SECTION 4 - shall be patentable inventions of products or processes, provided they are new, involve an inventive step and are capable of industrial application. a) For the purposes of this Act shall be considered an invention all human creation that allows to transform matter or energy for its exploitation by man. ARTICLE 6 – not to be considered inventions for the purposes of this law:

	a) Discoveries, scientific theories and mathematical methods; b) Literary or artistic works or any other aesthetic creation, as well as scientific works; c) Schemes, rules and methods for performing mental acts, playing games or for economic and business activities as well as computer programs; d) Methods of presenting information; e) Methods of surgical, therapeutic or applicable to the human body and those relating to animal diagnostic treatment; f) The juxtaposition of known inventions or mixtures of known products, variations in their form, dimensions or materials, except in the case of combination or merger such that they cannot function separately or that the qualities or functions of the thereof are modified to obtain an industrial result not obvious to a person skilled in the art; g) All types of living matter and substances preexisting in nature. ARTICLE 7 - are not patentable: a) Inventions whose exploitation within the territory of the REPUBLIC OF ARGENTINA must be prevented to protect public order or morality, health or life of humans or animals or to preserve plants or avoid serious damage to the environment; b) The entire biological and genetic material existing in nature or a replica thereof, in the biological processes implicit in animal, plant and human reproduction, including genetic processes involving material capable of conducting its own duplication in normal and such free as occurs in nature.
México	Industrial Property Law DOF 09-04-2012 Article 15. Invention is considered any human creation that allows to transform matter or energy existing in nature, for human use to meet their specific needs. Article 16. shall be patentable inventions that are new, involve an inventive step and capable of industrial application, in terms of this Act, except: I.-Essentially biological processes for the production, reproduction and propagation of plants and animals; II.- The biological and genetic material as found in nature; III. -Animal breeds; IV. - The human body and the living parts composing it, and V.- Plant varieties. ARTICLE 19.- not be considered inventions for the purposes of this Act: I. Theoretical or scientific principles; II. Discoveries that consist in making known or revealing something that already existed in nature, even though it was previously unknown to man; III. Schemes, plans, rules and methods for performing mental acts, playing games or doing business, and mathematical methods; IV. Computer programs; V. Methods of presenting information; VI. Aesthetic creations and artistic or literary works;

	VII. Methods of surgical, therapeutic or applicable to the human body and those relating to animal diagnostic treatment, and VIII. The juxtaposition of known inventions or mixtures of known products, or alteration of the use, form, dimensions or materials, except that in reality they are so combined or merged so that they cannot function separately or that the qualities or functions characteristic thereof are modified to obtain an industrial result or use not obvious to a person skilled in the art.
Brazil	Law 9279 Art. 8 - is patentable an invention that meets the requirements of novelty, inventive step and industrial application. Art. 10 - It is not considered inventions or utility models: I - discoveries, scientific theories and mathematical methods; II purely abstract concepts; III - schemes, plans, principles or commercial methods, accounting, financial, educational, publishing, lottery or fiscal nature; IV - literary, architectural, artistic and scientific works or any aesthetic creation; V - computer programs themselves; VI - presentation of information; VII - rules of games; VIII - surgical techniques and methods, as well as therapeutic or diagnostic methods, for use in the human body or animal; and IX - the All or part of natural living beings and biological materials found in nature or isolated there from, including the genotype of any living being and the natural biological processes. Art. 18 - are not patentable: I - that which is contrary to morals, good customs and public security, order and public health; II - substances, matter, mixtures, elements or products of any kind, as well as the modification of their physical-chemical properties and the respective processes of obtaining or modifying them, when resulting from transformation of the atomic nucleus; and III - the All or part of living beings, except transgenic microorganisms that meet the three requirements for patentability; novelty, inventive activity and industrial application - provided for in art. 8 and which are not mere discoveries. Sole Paragraph - For the purposes of this law, transgenic microorganisms are organisms, except the whole or part of plants or animals that express, through direct human intervention in their genetic composition, a characteristic normally not attainable by the species under natural conditions.

As shown in the above comparison chart, even though globally there are three universal requirements for assessing the patentability of a subject, in each country this subject to patent may be restricted to only three categories of protection, machinery and manufacturing processes , as shown by Costa Rican law Article 1 of Act 6867, which is consistent with the TRIPS Agreement, notwithstanding the foregoing, each country can provide protection to other categories such as

applications in the case of the EPO and the United States of America, or even business methods or strategies or software as in the case of the USPTO [13, 14, 15,17].

From the comparison of table 1 it's worth noting that each country has a different definition of patentability, in the case of Cuba this definition is quite specific, the more general is the United States of America and the European Patent Convention, in for Latin America, the Mexican definition is the widest of all. This table delimits the concept of eligibility and inventiveness which are different, the eligibility is defined by the law of each country on each matter is eligible for patent, as the inventiveness defines patentable subject matter as an invention by law, the European Patent Convention is influenced by the doctrine of eligibility but includes some restrictions own inventiveness.

It is clear that in the way in which invention is defined, the order in which the concept is placed, and the restrictions of each country must define what kind of influence group matter is patentable or not, the fact is defined as any subject patentable describing the US Federal Code gives an open definition, while Costa Rican legislation restricted to only two categories in this matter.

This is important because the first criterion is to determine whether a pharmaceutical product is an inventive polymorph, an inventive machine or an inventive manufacturing process to establish its patentability, but in the case also should be noted that not all products are inventions, for the event of Costa Rica, backed the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) as to be considered an invention must be for starters distinguished with undefined inventions of Law [13, 12].

In this case in Table 2 A comparison between the definition of invention and non-invention in Costa Rican legislation is shown, just as in the case of Argentina legislation, in the case of the definition of Mexican invention it is much more open despite the restrictions that Article 19 provides.

Table 2. Comparison of the concepts of invention, non-invention and exceptions for patentability in Law 6787 Costa Rica. [14]

Concept	Definition
Invention	- Invention is every creation of the human intellect, capable of being applied in industry, meeting the conditions for patentability under this law. It may be a product, a machine, a tool or a manufacturing process and will be protected by the patent.
Non invention	For the purposes of this law shall not be considered inventions: a) Discoveries, scientific theories, mathematical methods and computer programs in isolation. b) Purely aesthetic creations, literary and artistic works. c) Plans, principles or economic methods of advertisements or business and those referring to purely mental, intellectual or to games. d) The juxtaposition of known inventions or mixtures of known products, variations in their form or use, dimensions or materials, except in the case of a combination or merger such that they cannot function separately or that the qualities or functions of

	them are modified to obtain an industrial result not obvious to one skilled in the art.
Exceptions or Exclusions to Patentability	Excluded from patentability: a) Inventions whose commercial exploitation must be prevented objectively and necessarily to protect public order, morality, health or life of persons or animals or to preserve plants or to avoid severe damage to the environment. b) Methods of diagnostic, therapeutic and surgical methods for treating humans or animals. c) Plants and animals other than microorganisms, provided they are not microorganisms as found in nature d) Essentially biological processes for the production of plants or animals other than non-biological and microbiological processes.

As shown in Table 2 discoveries are not considered inventions, for example calcium carbonate in the wild would not be considered an invention as it is found as such in nature, including their various crystalline forms, but in the case whether drugs or biological products of chemical synthesis, Could it be assumed the same criteria, or not?. In other countries is defined which discoveries are patentable and which are not, while the European Patent Convention and the United States does not make this restriction, and no distinction is drawn respectively [1, 14].

It is at this point that the technical characteristics are important and must know in depth the process of forming the solid state to answer this question.

In the solidification process energy decreases because a cooling process depending on whether pure or not the substance to solidify. It may be first order, or higher, for this case will be discussed pure substances, in which phase transitions (i.e. the transition from one phase to another) defining a phase as a part of a system with the same physical and chemical properties, are of order one [10].

All substances known in the universe, regardless of their chemical nature crystallize in seven basic crystal systems ordinands. Based on these seven basic systems are generated the so called Bravais lattices which in total they are 232 and it depends on the rearrangement the atoms suffer in the seven basic networks [2,10].

These basic structures known as unit cells are shown in figure 1, from this information is important to understand that the crystalline forms are limited and predictable from the moment the molecule is known, however usually it depends on the conditions of crystallization or recrystallization of polymorph type occurring and its purity [2, 21, 22].

Often physicochemical characterization tests as x-ray diffraction, Raman spectroscopy, differential scanning calorimetry, infrared spectroscopy, etc. is used to define the technical characteristics of a polymorph, Figure 2 below shows an example of this characterization. Powder diffractometer Bruker X-ray was used to identify clearly two different forms of Clopidogrel bisulfate, repetitive crystalline lattices allow to determine a definite pattern of diffraction of the unit cells which are reflected in different peaks, different intensities of the peaks and displacement thereof [24].

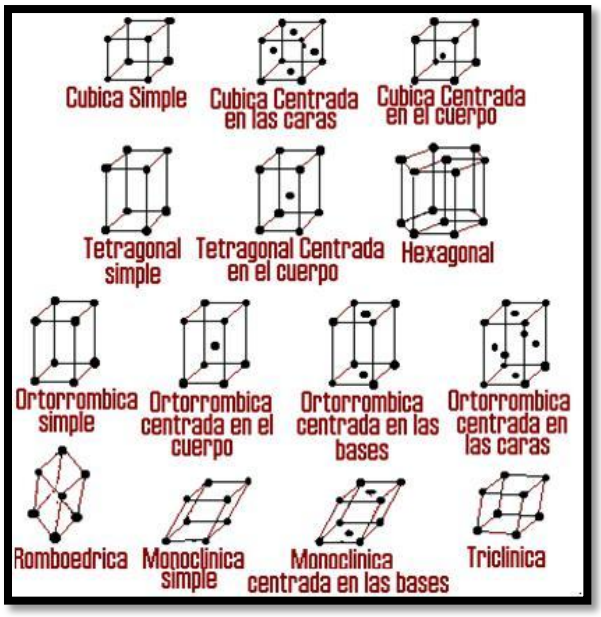
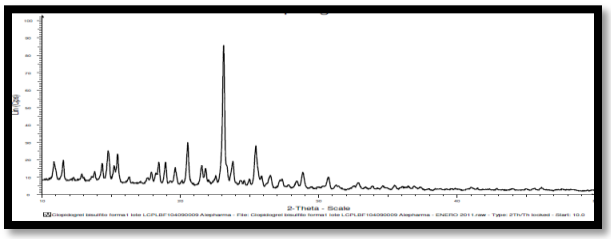
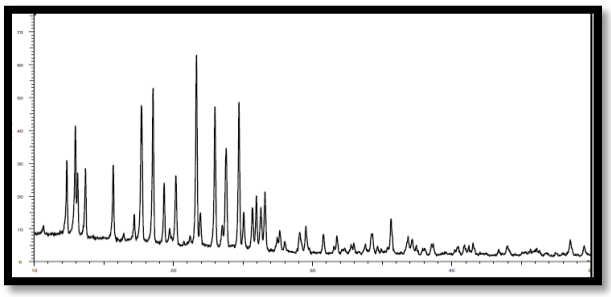


Figure 1. The seven crystal systems and fourteen basic networks Bravais derived [23].



A



B

Figure 2. X-ray diffractograms of Clopidogrel bisulfate A forms I and B forms 2. Source: conducted at the University of Costa Rica School of Chemistry with an X-ray diffractometer Bruker D8 [25].

However, the characterization of this form is not complete because it omits the fact of the influence of impurities including impurity of other polymorphs, the shape of the crystal habit, and even forget that the technical effect of the active ingredient cannot be separated from the pharmaceutical form, as in the case of Costa Rica the use is not a category of invention, and therefore the second uses would not be patentable.

Bernstein on this point indicates that paracetamol is available in two main forms I and II. The I occupy binders in the formulation while form II does not however form II spontaneously transforms into the form I, that is to say the coexistence in the pharmaceutical form [14, 22].

That is to saya complete characterization should also include the dosage form, since the active substance may undergo phase transformations in the manufacturing process.

In this case the main technical characteristics to evaluate in a pharmaceutical polymorph, are not so much the characterization tests, although these can be useful for quick identification, but rather the angles of the crystal lattice and space groups, i.e. its definition in one of the 232 crystalline lattices, and complementary patterns of x-ray diffraction, melting thermograms actually, experts in the subject recommend best characterize polymorph to verify their existence, however, this fact is not usually met by applicants, as a complete and specific characterization diminishes the possible scope of protection and even practically precludesa claim of patent violation, as current analytical techniques do not identify with the same accuracy and precision within a crystalline form of a dosage form due to interactions suffering this with the other components of the formulation [2].

Then, after analyzing these points it is important to understand the difference between an invention and discovery, as both can be products and possess technical characteristics, however the

main difference is in implied novelty, since a discovery in nature, meaning nature everything that is independent of the will of man, and that man is using a deductive methodology [1, 25].

An invention is characterized by being found by an inductive approach, this can be summarized in Figure 3 wherein the steps of an invention and a discovery are displayed.

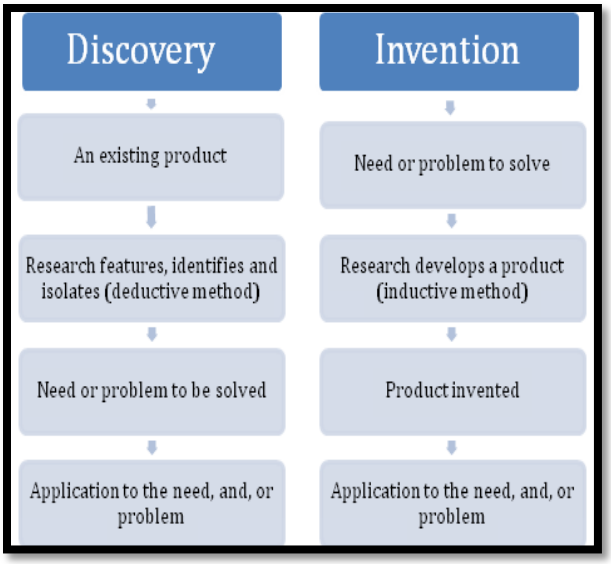
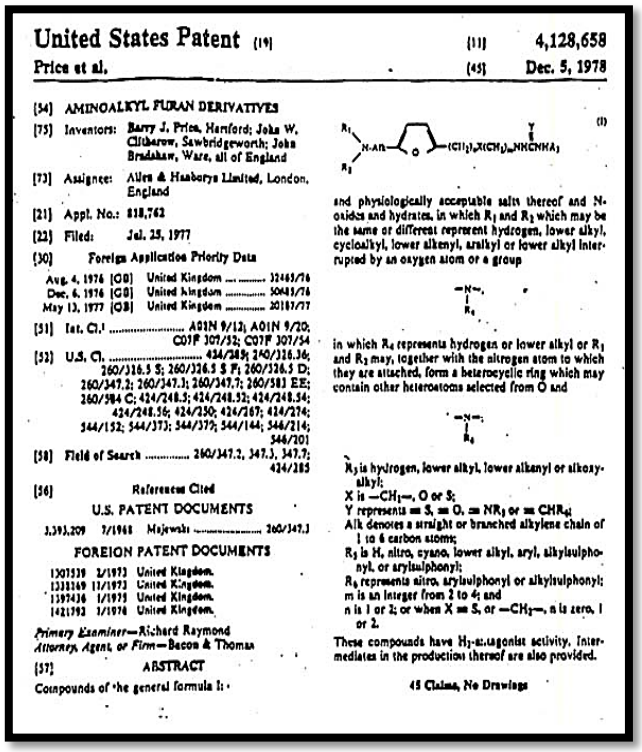


Figure 3. Comparative Scheme between the concepts of invention and discovery. Source: made by the author in Office Word 2013 ®

In a breakthrough product exists and the investigator finds it by trial and error techniques without knowing the exact nature and then gives it an application or more, this doctrine is known as serendipity which is discussed later [1, 5].

In the case of an invention the desired product or procedure does not exist prior, but the researcher wants to obtain it with certain technical characteristics which he has planned because he knows their main application or use. That is why using a systematic action induced by the investigator or desired process product is obtained [25].

This fundamental difference, always confused with the technical difficulty or obviousness, almost always by an economic reason or temporary properly assessed in the inventive level requirement of patentability which is only assessable for inventions and not discoveries, in the case of Costa Rican law, unlike the US legislation if allowed as eligible subject to patent discoveries (see Table 1), therefore non-obviousness of one of the characteristics to evaluate level between the inventive, it is evaluable in US law for the case of pharmaceutical polymorphs.


United States Patent [19] [11] 4,128,658
Price et al. [45] Dec. 5, 1978

[54] AMINOALKYL FURAN DERIVATIVES

[75] Inventors: Barry J. Price, Hanford; John W. Clitherow, Sawbridgeworth; John Bradshaw, Ware, all of England

[73] Assignee: Allen & Hanburys Limited, London, England

[21] Appl. No.: 818,762

[22] Filed: Jul. 25, 1977

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Dec. 6, 1976 [GB] United Kingdom 50483/76
May 13, 1977 [GB] United Kingdom 20197/77

[51] Int. Cl.² A01N 9/12; A01N 9/20; C07F 307/52; C07F 307/54

[52] U.S. Cl. ..... 424/285; 260/326.36; 260/326.5 S; 260/326.5 F; 260/326.5 D; 260/347.2; 260/347.3; 260/347.7; 260/583 EE; 260/584 C; 424/248.3; 424/248.52; 424/248.54; 424/248.56; 424/250; 424/267; 424/274; 544/152; 544/373; 544/379; 544/144; 544/214; 546/201

[58] Field of Search 260/347.2, 347.3, 347.7; 424/285

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1421792 1/1976 United Kingdom.

Primary Examiner—Richard Raymond
Attorney, Agent, or Firm—Bacon & Thomas

[57] ABSTRACT

Compounds of the general formula I:

(I)

and physiologically acceptable salts thereof and N-oxides and hydrates, in which R_1 and R_2 which may be the same or different represent hydrogen, lower alkyl, cycloalkyl, lower alkenyl, aralkyl or lower alkyl interrupted by an oxygen atom or a group

in which R_4 represents hydrogen or lower alkyl or R_1 and R_2 may, together with the nitrogen atom to which they are attached, form a heterocyclic ring which may contain other heteroatoms selected from O and

R_3 is hydrogen, lower alkyl, lower alkanyl or alkoxyalkyl;
X is $-CH_2-$, O or S;
Y represents $=S$, $=O$, $=NR_4$ or $=CHR_4$;
Alk denotes a straight or branched alkylene chain of 1 to 6 carbon atoms;
R_5 is H, nitro, cyano, lower alkyl, aryl, alkylsulphonyl, or arylsulphonyl;
R_6 represents nitro, arylsulphonyl or alkylsulphonyl;
m is an integer from 2 to 4; and
n is 1 or 2; or when X = S, or $-CH_2-$, n is zero, 1 or 2.

These compounds have H_2-antagonist activity. Intermediates in the production thereof are also provided.

45 Claims, No Drawings

Figure 4. First page of the polymorph patent Ranitidine Hydrochloride generated by the doctrine of serendipity [30].

The American doctrine defined for many years that pharmaceutical polymorphs are discoveries, the Supreme Court of the United States has, however denied patentability only in cases of non-obviousness and lack of novelty, because

their legislation and case law allows the protection of discoveries, moreover, it defined the polymorphs found by serendipity unpatentable because of the obviousness of their production, as was the famous case of Ranitidine Hydrochloride [26].

The following table summarizes some of the main polymorphism doctrines of the United States of America where the main criterion is stated that defined the resolution of the court, such comparative studies have been conducted by Dr. Joel Bernstein a specialist in chemical patents, which has studied the issue at length

Table 3. Comparison of cases of the doctrine of patents and pharmaceutical polymorphs. [26, 27, 28, 29, 30, 31, 32, 33]

Case	Criterion
Ranitidine Hydrochloride Glaxo vs Novopharma Supreme Court of the United States of America	The court defined for the polymorphic concept of serendipity that is to say a fortuitous discovery and recognition of polymorphs, also described the role of solvent, heating, agitation, etc. to control the polymorph obtained, he said the development and use of analytical methods for the characterization of polymorphs spoke about the relative stability of polymorphs, also discussed the phenomenon of disappearing polymorphs defined the role of planting, intentional and unintentional . He distinguished between polymorphic identity and purity, the end indicated that Novopharm did not violate the patent and that it was cancelled.
Paroxetine Hydrochloride SmithKline BeechamSupreme Court of the United States of America	In summary, the Supreme Court overturns the claim construction of the district court, and he argues that the claim 1 covers the form of crystalline paroxetine hydrochloride hemihydrate without limitation. affirms the district court's conclusion that anhydrous product Apotex I "Notwithstanding this conclusion, the court held, on the basis of the undisputed facts, that clinical trials of SmithKline constituted a public use under § 102 (b) provision of valid claim 1. Apotex is therefore not liable for infringement of claim 1 of the '723'. Infringes claim 1 under that broad interpretation.. "This case described the practical and formal legal definition anhydrate and hemihydrate, the chemical and physical characterization of an anhydrate and hemihydrate, the relative stability of hemihydrate and anhydrate described in the conversion factors anhydrate to hemihydrate, features and role seeding intentional and unintentional in the crystallization process, and the qualitative and quantitative analytical methods for determining the composition and crystalline mixture.
Bristol Myers Cefadroxil vs Zenith Supreme Court of Justice of the United States of America	It described the case as serendipity, Zenith is accused of violating the patent for Bristol Myers Zenith hemihydrate tends to become the monohydrate form in the stomach, Bristol Myers indicates that found 15 of the 37 diffraction patterns of Zenith sample, the Supreme Court pointed out that 15 of 37 diffraction lines are not enough to infringe the patent, the highlights are non-infringement by not having complete characterization and confirmation of serendipity discoveries in case of polymorphs.

Aspartame Searle vs Ajinomoto EPO Board Apellation	It describes and defines the term of crystal habit, describes the offense if there is not the same complete characterization even the same polymorph, describes the process of serendipity
Atorvastatina Pfizer Inc. vs Teva pharmaceuticals Board Apellation EPO	Patent polymorphic forms of atorvastatin for lack of inventive step was invalidated.
Imatinib Mesilato / Gleevec Novartis vs. Union of India IPAB (Intellectual Property Appellate Board)India	The case originated in a request from the Novartis patent for Gleevec product and the presentation of five competitions Based on the Indian law does not permit the patenting of medicines that are not considered completely new. Based on this foundation, the application is rejected, the reason why Novartis submitted written in the Madras High Court challenging the rejection of his application and constitutional norms that founded the rejection. The IPAB dismissed the appeal and held that Gleevec was not patentable and that its market price was excessive.
Paroxetine methane sulfonate Synthon vs. Smithkline House of Lords United Kingdom	The applicant requests to revoke the defendant patent for disability considering that claim 1 was anticipated in their patent application. The trial judge declared the invalidity of the patent. The defendant appealed and the Court of Appeal reversed the judgment on the ground that the invention was not obvious to the man in the office of ordinary skill. Finally, the defendant appealed to the House of Lords and it overturned the original ruling and declared the patent invalid for lack of novelty.
Rutinamida Novartis vs INPI Argentina Chamber III of the Court of Appeals in Federal Civil and Commercial Argentina	The statement stressed that did not comply with the requirement of inventive step in that Novartis did not provide comparative data showing alleged significant improvements of the polymorph patent that was intended. About it he noted that the inventive concept is determined not according to what the inventor has done to reach its inception, but based on "objective differences it has with respect to the existing technology." Therefore, "inventive step involves comparing the state of the art with the alleged invention and the assessment as to whether the differences between the two are obvious to a person skilled in the technical field".
Olanzapina Elli Lilly Company vs Gutis S.A Patent invalidity National Registry of Property Costa Rica	The patent was cancelled for lack of novelty inventive step and be considered a discovery, the applicant also gave up the priority claimed.
Rimonabant Sanofi vs ALAFAR Opposition IEPI Ecuador	Lack of novelty defined and inventiveness of the polymorph, polymorph is defined as not patentable because it is a discovery, and also a change of form.

In January 2014 a revolutionary study was published in Japan among Japanese scientists and expert in Spanish crystallization Juan Manuel Garcia Ruiz, in which they managed to find a methodology to assess all crystalline forms that can generate a substance from the moment that is synthesized, the study published in

Journal of American Chemical Society, the main conclusions which describes this publication is that all possible crystalline forms of a substance coexist from the time that the molecule is synthesized, and what happens is one or the other prevails greater or lesser extent depending on the environment [34].

This fact and other exposed justify the definition of a pharmaceutical polymorph discovered as a product and not an inventive products the main feature of a discovery is his pre-existence in nature that is the implicit existence before the priority claimed, when existing this first begins to be in the nature and this gives their starting prexistence because after this first discovery polymorphs stop having implicit existence to existence explicitly, as shown in experiments from Garcia Ruiz [1, 2,32, 33, 34, 35].

After the date of synthesis of the compound, their polymorphs are affected by their existence, regardless of whether the original product was invented, the ways this is accommodated in the space groups are a discovery, since the existence of the molecule assumes the existence of all the different crystal forms, just as he demonstrated by the experiment of García Ruiz, who explains that what is given back to its synthesis, is a process of serendipity to purify and identify different crystalline forms in different optimal crystallization conditions [1, 2, 32, 33 , 34, 35].

Some people confuse the fact of the difficulty of obtaining a polymorph, or purifying it, or the fact that its production or purification involves a human act, with the possibility of patenting the same, this analysis avoids a fundamental point of the technical evaluation of patents, which is the non-commutativity of the process, i.e. it is followed a direction of processing each stage and these cannot skip or anticipate that affect severely the final result [32].

On non-procedural commutativity of the technical report, more precisely to the case of study, it explains that you cannot evaluate the characteristics of the inventive and the difficulty level, without having defined eligibility according to the Anglo-Saxon doctrine, or inventiveness according to the Roman doctrine of the matter in question, that is to say you must first know whether the study is patentable within the initial restrictions of each country or jurisdiction, then the unit of invention of possible subject to patent, then clarity, then its adequacy should be assessed and finally the requirements called traditionally basic such as novelty, inventive step and industrial application, in that order.

To not follow this order, could generate the kind of confusion generated with pharmaceutical polymorphs, where the difficulty of obtaining it is argued as a basis to apply for patentability, ignoring the restriction to be a discovery of pre-existing matter in nature.

The other concept, as indicated is human intervention in a discovery to deduce the patentability of a polymorph, is exposed in the following way, it has become clear in the doctrine of the United States of America that if you allow the patenting of discoveries when it has an act of human intervention, based on this fact occasions the patentability of polymorphs in North America, as they are eligible for patenting, however Costa Rican law does not consider inventions to any discoveries, as explained the main features of a discovery are pre-existence in nature having this prexistencia the basis of the priority date claimed by the application and obtaining intellectual process is deductive character, because regardless of any discovery there

is always human intervention and that is what makes his life goes from being implicit to become explicit [25, 26, 32].

Conclusions

In conclusion, we can say that the polymorphs are due to a deductive process, when the matter of which they proceed exists before the priority date, therefore are pre-existing in nature, this makes in Costa Rican law not possible to protect a polymorph when such matters of origin prexiste to the priority date, however if the polymorphic form is registered at the same time that the principle is active claim that is to say enjoy the same priority date their requirements for patentability should be evaluated not as preexisting in nature but coexisting at the same point of synthesis.

In any case if a polymorph could be protected, i.e. not previously existed in nature, could only occur as not crystallize in the seven basic systems or fourteen Bravais lattices, or in the case of identification at the time of synthesizing a patentable compound, in both cases the complete characterization of a polymorph is the only way to assess its patentability, for this the combination of a series of tests such as X-ray diffraction, infrared spectroscopy, and Raman spectroscopy, differential scanning calorimetry, among other analytical techniques it is essential to give sustenance to the invention as a single technique is not enough for a complete description of a polymorph, also the polymorphic forms in the pharmaceutical carrier and the final dosage form must also be assessed.

The Doctrine of the Supreme Court of the United States of America in several cases has reinforced the fact that the polymorphs are discoveries and their identification is a serendipitous act which confirms the fact of their non-patentability in countries where these are not patentable nevertheless even in those jurisdictions where the discoveries are patentable, lack of novelty and obviousness have made many of these patents be granted or not reversed.

Finally, the fact that in several countries with Roman law, the patentability of polymorphs is considered, mainly due to an incorrect interpretation of the eligibility criteria of inventiveness, or the concept of total judicial review wherein the total assessment is required the application despite its non-patentability not to affect the rights of the administered

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