Appeal decision

Appeal No. 2014- 24987

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The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2011-529360, entitled "IMPLANTABLE DEVICE FOR THE DELIVERY OF RISPERIDONE AND METHODS OF USE THEREOF" [April 8, 2010 international publication, International Publication No. WO 2010/039722, February 16, 2012 National Publication, National Publication of International Patent Application No. 2012-504146] has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

1. History of the procedures

The present application was filed on September 29, 2009 (priority claim under the Paris Convention: September 30, 2008 (US), November 24, 2008 (US)) as an international filing date, a notification of reasons for refusal was issued on November 7, 2013, and, responding to the notification, a written argument and a written amendment were submitted on February 12, 2014. A decision for refusal was issued on July 30, 2014, an appeal against an examiner's decision of refusal was requestedon December 5, 2014, and the statement of the request in the appeal was amended on December 24, 2014.

2. The Invention

The invention according to Claim 1 (hereinafter, referred to as "the Invention".) is specified by matters described in Claim 1 in the scope of claims in the written amendment submitted on February 12, 2014, as follows.

"A drug delivery device for the controlled release of risperidone over an extended period of time to produce local or systemic pharmacological effects, comprising:

a) a polyurethane-based polymer formed to define a hollow space; and

b) a solid drug formulation comprising a formulation comprising risperidone and optionally one or more pharmaceutically acceptable carriers,

wherein the solid drug formulation is contained in the hollow space, and

wherein the device provides a desired release rate of risperidone from the device after implantation."

3. Described matters in Cited Documents

A. Cited Document A

Cited Document A (National Publication of International Patent Application No. 2007-502139, Document 2 in the reasons for refusal of the examiner's decision)=cited in the reasons for refusal of the examiner's decision in the original examination, which was distributed before the priority date of the present application, contains the following descriptions.

(A) "Drug delivery device for releasing one or more drugs at controlled rates for an extended period of time to produce local or systemic pharmacological effects, said drug delivery device having a reservoir comprising:

i. at least one active ingredient; and, optionally,

ii. at least one pharmaceutically acceptable carrier; and

iii. a polyurethane based polymer completely surrounding the reservoir." (Claim 1)

(B) "[0001]

The present invention relates to the field of drug delivery devices and more specifically implantable drug delivery devices made of polyurethane based polymers." (Paragraph [0001])

(C) "[0007]

SUMMARY OF THE INVENTION

It is an object of the present invention to provide polyurethane based long term drug delivery devices.

[0008]

It is a further object of the present invention to provide biocompatible and biostable polyurethane based devices for the delivery of drugs or other compounds in a living organism." (Paragraphs [0007] and [0008])

(D) "[0033]

To take the advantage of the excellent properties of polyurethane based polymers, this invention uses polyurethane based polymers as drug delivery devices for releasing drugs at controlled rates for an extended period of time to produce local or systemic pharmacological effects. The drug delivery device preferably comprises a cylindrically shaped reservoir surrounded by polyurethane based polymer through which the delivery rate of the drug inside the reservoir is controlled. The reservoir comprises active ingredients and, optionally, pharmaceutically acceptable carriers. The carriers are formulated to facilitate the diffusion of the active ingredients through the polymer and to ensure the stability of the drugs inside the reservoir.

[0034]

The present invention provides a drug delivery device that can achieve the following objectives: a controlled release rate (zero order release rate) to maximize therapeutic effects and minimize unwanted side effects; an easy way to retrieve the

device if it is necessary to end the treatment; an increase in bioavailability with less variation in absorption; and no first pass metabolism.

[0035]

The release rate of the drug is governed by Fick's Law of Diffusion as applied to a cylindrically shaped reservoir device (cartridge). The following equation describes the relationship between different parameters:

[0036]

[Expression 1]

$$\frac{dM}{dt} = \frac{2\pi h p \Delta C}{\ln (r_0/r_j)}$$

[0037]

where

[0038]

[Expression 2]

$\frac{dM}{dt}$: 薬剤放出率

h : 装置の充填部分の長さ

ΔC : 容器壁を横切る濃度勾配

r_0/r_j : 装置の内径に対する外径の割合

p : 使用されたポリマーの透過係数

薬剤放出率　drug release rate

装置の充填部分の長さ　　length of filled portion of device

容器壁を横切る濃度勾配　concentration gradient across the reservoir wall
装置の内径に対する外径の割合　ratio of outside to inside radii of device
使用されたポリマーの透過係数　permeability coefficient of the polymer used

[0039]

The permeability coefficient is primarily regulated by the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of drug and the polymer. Once the polymer and the active ingredient are selected, p will be a constant, and h, ro, and ri are fixed and kept constant once the cylindrically shaped device is produced. Δ C is maintained constant by the carriers inside the reservoir.

[0040]

To keep the geometry of the device as precise as possible, the preferably cylindrically shaped device can be manufactured through a precision extrusion or precision molding process for thermoplastic polyurethane polymers, and reaction injection molding or spin casting process for thermosetting polyurethane polymers.

[0041]

The cartridge can be made with either one end closed or both ends open. The open end can be plugged with a pre-manufactured end plug to ensure a smooth end and a solid seal. The solid active ingredient and carriers can be compressed into pellet form to maximize the loading of the active ingredient. (Paragraphs [0033] to [0041])

(E) "[0043]

Once the cartridges are sealed on both ends with filled reservoir, they are conditioned and primed for an appropriate period of time to ensure a constant delivery rate.

[0044]

The conditioning of the drug delivery devices involves the loading of the active ingredient (drug) into the polyurethane based polymer which surrounds the reservoir. The priming is done to stop the loading of the drug into the polyurethane based polymer and thus prevent loss of the active ingredient before the actual use of the implant. The conditions used for the conditioning and priming step depend on the active ingredient, the temperature, and the medium in which they are carried out. The conditions for the conditioning and priming may be the same in some instances.

[0045]

The conditioning and priming step in the process of the preparation of the drug delivery device is done to obtain a determined rate of release of a specific drug. The conditioning and priming step of the implant containing a hydrophilic drug is preferably carried out in an aqueous medium, more preferably in a saline solution. The conditioning and priming step of a drug delivery device comprising a hydrophobic drug is usually carried out in a hydrophobic medium such as an oil based medium. The conditioning and priming steps are carried out by controlling three specific factors; namely, the temperature, the medium, and the period of time.

[0046]

A person skilled in the art would understand that the conditioning and priming step of the drug delivery device will be affected by the medium in which the device is placed. As mentioned previously, a hydrophilic drug would be preferably conditioned and primed in an aqueous solution, and more preferably, in a saline solution. For example, Histrelin and Naltrexone implants have been conditioned and primed in saline solution, more specifically, conditioned in saline solution of 0.9% sodium content and primed in saline solution of 1.8% sodium chloride content." (Paragraphs [0043] to [0046])

(F) "[0053]

"The drug (active ingredient) that can be delivered includes drugs that can act on the central nervous system, psychic energizers, tranquilizers, anti-convulsants, muscle relaxants, anti-parkinson, analgesic, anti-inflammatory, anesthetic, antispasmodic, muscle contractants, anti-microbials, anti-malarials, hormonal agents, sympathomimetic, cardiovascular, diuretics, anti-parasitic and the like." (Paragraph [0053])

(G) "[0059]

Different functional groups can be introduced into the polyurethane polymer chains through the modification of the backbones of polyols, depending on the properties desired. When the device is used for the delivery of water soluble drugs, hydrophilic pendant groups such as ionic, carboxyl, ether, and hydroxy groups are incorporated into the polyols to increase the hydrophilicity of the polymer (e.g. U.S. patents 4,743,673 and 5,354,835). When the device is used for the delivery of hydrophobic drugs, hydrophobic pendant groups such as alkyl, siloxane groups are incorporated into the polyols to increase the hydrophobicity of the polymer (e.g. U.S. patent 6,313,254). The release rates of the active ingredients can also be controlled by the hydrophilicity/hydrophobicity of the polyurethane polymers." (Paragraph [0059])

(H) "[0060]

Once the appropriate polyurethane polymer is chosen, the next step is to determine the best method to fabricate the cylindrically shaped implants.

[0061]

For thermoplastic polyurethanes, precision extrusion and injection molding are the preferred choices to produce two open-end hollow tubes (see Figure 1) with consistent physical dimensions. The reservoir can be loaded freely with appropriate formulations containing active ingredients and carriers or filled with pre-fabricated pellets to maximize the loading of the active ingredients. One open end needs to be sealed first before the loading of the formulation into the hollow tube. To seal the two open ends, two pre-fabricated end plugs (see Figure 2) are used. The sealing step can be accomplished through the application of heat or solvent or any other means to seal the ends, preferably permanently.

[0062]

For thermoset polyurethanes, precision reaction injection molding or spin casting is the preferred choice, depending on the curing mechanism. Reaction injection molding is used if the curing mechanism is carried out through heat, and spin casting is used if the curing mechanism is carried out through light and/or heat. Preferably, hollow tubes with one open end (see Figure 3) are made by spin casting. Preferably, hollow tubes with two open ends are made by reaction injection molding. The reservoir can be loaded in the same way as the thermoplastic polyurethanes.

[0063]

Preferably, to seal an open end, an appropriate light-initiated and/or heat-initiated thermoset polyurethane formulation is used to fill the open end, and this is cured with light and/or heat.

[0064]

More preferably, a pre-fabricated end plug can also be used to seal the open end by applying an appropriate light-initiated and/or heat-initiated thermoset polyurethane formulation on to the interface between the pre-fabricated end plug and the open end and curing it with the light and/or heat or any other means to seal the ends, preferably permanently.

[0065]

The final process involves the conditioning and priming of the implants to achieve the delivery rates required for the active ingredients. Depending upon the types of active ingredient, hydrophilic or hydrophobic, the appropriate conditioning and

priming media will be chosen. Water based media are preferred for hydrophilic active ingredients and oil based media are preferred for hydrophobic active ingredients.
[0066]

As a person skilled in the art would readily know, many changes can be made to the preferred embodiments of the invention without departing from the scope thereof. It is intended that all matter contained herein be considered illustrative of the invention and not in a limiting sense." (Paragraphs [0060] to [0066])

(I)

【図１】

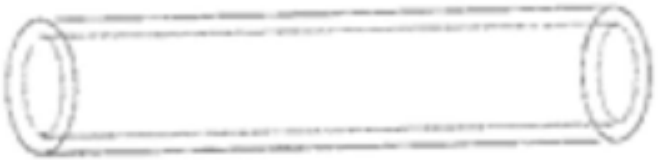


Figure 1

【図２】

Figure 2

【図３】

Figure 3

(Figures 1-3)

(J) "[Example 1]

[0067]

Tecophilic polyurethane polymer tubes are supplied by Thermedics Polymer Products and manufactured through a precision extrusion process. Tecophilic polyurethane is a family of aliphatic polyether-based thermoplastic polyurethane which can be formulated to different equilibrium water contents of up to 150% of the weight of dry resin. Extrusion grade formulations are designed to provide maximum physical properties of thermoformed tubing or other components.

(Omission)

Hp-60D-20 is extruded to tubes with thickness of 0.30 mm with inside diameter of 1.75 mm. The tubes are then cut into 25 mm in length. One side of the tube is sealed with heat using a heat sealer. The sealing time is less than 1 minute. Four pellets of histrelin acetate are loaded into the tube. Each pellet weighs approximately 13.5 mg for a total of 54 mg. Each pellet comprises a mixture of 98% histrelin and 2% stearic acid. The second end open of the tube is sealed with heat in the same way as for the first end. The loaded implant is then conditioned and primed. The conditioning takes place at room temperature in a 0.9% saline solution for 1 day. Upon completion of the conditioning, the implant undergoes priming. The priming takes place at room temperature in a 1.8% saline solution for 1 day. Each implant is tested in vitro in a medium selected to mimic the pH found in the human body. The temperature of the selected medium is kept at approximately 37°C during the testing. The release rates are shown in Figure 4." (Paragraphs [0067] to [0070])

(K) "[Example 2]

[0072]

HP-60D-35 is extruded to tubes with thickness of 0.30 mm with inside diameter of 1.75 mm. The tubes are then cut into 32 mm in length. One side of the tube is sealed with heat using a heat sealer. The sealing time is less than 1 minute. Six pellets of naltrexone are loaded into the tubes and both open sides of the tubes are sealed with heat. Each pellet weighs approximately 15.0 mg for a total of 91 mg. The second end open of the tube is sealed with heat in the same way as for the first end. The loaded implant is then conditioned and primed. The conditioning takes place at room temperature in a 0.9% saline solution for 1 week. Upon completion of the conditioning, the implant undergoes priming. The priming takes place at room temperature in a 1.8% saline solution for 1 week. Each implant is tested in vitro in a medium selected to mimic the pH found in the human body. The temperature of the selected medium is

kept at approximately 37°C during the testing. The release rates are shown in Figure 5." (Paragraph [0072])

B. Cited Document B

Cited Document B (International Publication No. 2008/070118, Document 1 in the aforementioned written reasons for refusal) cited in the reasons for refusal of the examiner's decision in the original examination , which was distributed before the priority date of the present application, contains the following descriptions. Since Cited Document B is an English document, the Japanese Patent Document corresponding to Cited Document B, National Publication of International Patent Application No. 2010-511713 Official Gazette (hereinafter, referred to as "corresponding document.") is cited as a Japanese translation.

(A) "1. A pharmaceutical formulation comprising a drug and at least one CYSC polymer as hereinbefore defined." (Claim 1)

(B) "5. The formulation of claim 1 wherein the CYSC polymer is selected from the group consisting of: a poly-acrylate, a poly-methacrylate, a poly-alkyl-methacrylate, a poly-N alkylmethacrylamide, a poly-alkyl-acrylate, a poly-fluoroacrylate, a poly-N-alkyl acrylamide, a poly-alkyl oxazoline, a poly-alkyl vinyl ether, a poly-alkyl-1,2-epoxide, a poly-alkyl glycidyl ether, a poly-vinyl ester, a poly-acrylamide, a poly-methacrylamide, a poly-maleimide, a poly-α-olefin, a poly-p-alkyl styrene, a poly-alkylvinyl ethers, a polyether, a polyester, a polycarbonate, a polyphosphate, a polyurethane, a polysilane, a polysiloxane, and a poly-alkyl phosphazene." (Claim 5)

(C) "18. The formulation of claim 1 wherein the drug is selected from the group consisting of anti-pain medications, anti-psychotics, anti-inflammatories, hormones, cholesterol lowering drugs, anti-osteoporosis drugs, anti-angeogenics and contraceptives.
19. The formulation of claim 18 wherein in vivo, when implanted within a subject, the formulation continuously releases a therapeutically effective dose of drug to the subject over a period of at least 30 days.
20. The formulation of claim 18 wherein the drug is Risperidone or a pharmacologically active derivative, congener or metabolite thereof." (Claims 18-20)

(D) "FIELD OF THE INVENTION

This invention relates to polymeric systems for the delivery of drugs. There are many known polymeric systems for the delivery of drugs. A continuing problem is obtaining a desired rate of delivery at a desired location and at a desired time. The desired rate may be, for example, a steady rate over a relatively long period of time, and/or a relatively rapid rate over a relatively short period of time ("bolus" delivery).

SUMMARY OF THE INVENTION

We have discovered, in accordance with the present invention, that useful delivery of drugs can be obtained through the association of drugs with certain polymers which are referred to herein as CYSC polymers (an abbreviation for crystallizable side chain polymers)." (p.1, l.10-20, Paragraphs [0002] to [0004] in the corresponding document)

(E) "The term "CYSC polymer" (an abbreviation for crystalline side chain polymer) is defined herein as a polymer which

(1) comprises at least one moiety which

(i) has the formula

--b—Cy--

(ii) forms part of a repeating unit which

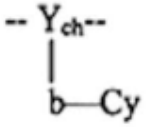
(a) provides at least part of the polymeric backbone of the polymer

and

(b) has formula (1) below,

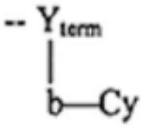
and/or

(iii) forms at least part of a terminal unit of the polymer backbone which has the formula (2) below



(1)

and



(2)

where YCh is a divalent moiety forming part of the backbone of the CYSC polymer,

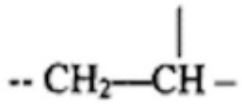
Yterm is a monovalent moiety at the end of the backbone of the CYSC polymer,

b is a bond or a divalent moiety linking the Cy moiety to the polymerbackbone, and

Cy is a monovalent moiety which is capable of associating with othermoieties (which may also be Cy moieties) to provide the CYSC polymer with crystallinity; and

(B) has a crystalline melting temperature, Tp, of at least 0°C and a heat of fusion of at least 5 J/g which results from the association of the Cy moiety (Tp and heat of fusion being measured on a DSC as hereinafter described).

The moiety —b--Cy is also referred to in this specification as an --Rc moiety; i.e., Rc is synonymous with —b--Cy. The CYSC polymers which contain a moiety of formula (2) above are sometimes referred to in this specification as end capped (ECC) polymers. The moieties YCh, Yterm, b, and Cy can be of any kind, and in CYSC polymers containing more than one moiety of formula (1) and/or more than one moiety of formula (2), YCh, Yterm, b, and Cy can be the same or different. A wide variety of such moieties are described below. The CYSC polymer can optionally contain, in addition to the moieties of formula (1) and (2), repeating units and/or terminal units having a different formula. Purely by way of example, YCh can be a



moiety, Yterm can be a --CH2—CH2— moiety, b can be a -CO2 - moiety, and Cy can be an n-alkyl moiety containing 18 carbon atoms.
Where reference is made in this specification to a moiety of formula —Y— or —Y(bCy) — or — (Rc)--, --Y-- can be Ych or Yterm." (p.2, l.5 to p.3. l.18, Paragraphs [0006] to [0011] in the corresponding document)

(F) "A drug associated with a CYSC polymer can for example be delivered at a controlled rate and/or at a desired location, the rate and/or the location being influenced for example by a chemical and/or physical condition which modifies the association of the drug and the CYSC polymer. The condition can for example be an environment which causes the CYSC polymer to undergo a chemical change (for example the weakening or creation of any kind of chemical association, e.g. oxidation, reduction, or hydration) and/or a change in physical state (for example the weakening or creation of any kind of physical association, e.g. a change in viscosity resulting from melting or crystallization, for example caused by internal or external heating) including an environment having a particular pH range, the presence of an enzyme. The term 'controlled rate' includes, but is not limited to, a continuous, sustained rate, an increasing or decreasing rate, continuous or discontinuous release, or maintenance of a substantially constant rate. The drug may be released, for example, with zero-, first- or second-order release kinetics." (p.3, l.19-30, Paragraph [0012] in the corresponding document)

(G) "In a typical embodiment of the invention, a therapeutic dose of the drug as

measured by plasma concentration (but alternatively as measured by clinical measurements) will be released over a period of time ranging from at least an hour to at least twelve months. Exemplary drugs suitable for sustained release include, for example, anti-pain medications (e.g. morphine analogues), anti-psychotics (e.g. risperidone), anti-inflammatories (e.g. steroids or NSAIDs), cholesterol lowering drugs (e.g., statins), osteoporosis drugs (biphosphonates), anti-angeogenics (e.g., anti-VEGF) and contraceptives. In the case of certain drugs such as contraceptives and osteoporosis drugs, sustained release may be desirable over a period of more than a year, for example at least 2, 3, 4, or 5 years. Prior formulations (Norplant) have been used to deliver a therapeutic dose of contraceptives over a period of three years. Long term sustained release formulations will generally be formulated for implantation within the body, e.g., subcutaneously.

The amount (weight) of drug released over a period of time will of course be related to therapeutically effective plasma concentration of the drug, the potency of the drug and drug kinetics including the residence time in the various tissues of interest and the rate of clearing. In use, the rate of release of a drug from the pharmaceutical composition of the invention may be no greater than, for example 10 ng per hour, or alternatively, 50 ng, 100 ng, 500 ng, 1000 ng, 2500 ng, or 5000 ng or in other embodiments, no more than 10 μg, 50 μg or 100 μg or 500 μg or 1000 μg per hour during the first 6 (or 12 or 24 or 36) hours following implantation. Of course, the desired rate of release of the drug will depend on its potency, its therapeutic window and its half-life. For example, Risperidone may be released over a period of time to provide a serum concentration of about 15 ng/ml up to about 100 ng/ml. A release of about 4 mg/day (or in other studies between 1 and 60 mg/day) is found to provide adequate therapeutic serum levels of Risperidone." (p.51, l.21 to p.52, l.12, Paragraphs [0185] and [0186] in the corresponding document)

(H) One specific example of a formulation containing the psychoactive (antipsychotic) agent Risperidone, (4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl]ethyl]-3-methyl-2,6-diazabicyclo[4.4.0]deca-1,3-dien-5-one) is the following. Risperidone may be physically mixed with a CYSC polymer, or may be pre-associated, for example with a surfactant, PEG, human (or bovine etc.) serum albumin, or with proteins etc. to provide immunological shielding, increased half-life, and improved bioavailability. The formulation may be formed into a shaped solid implant suitable for introduction, e.g. by trocar, under the skin or intramuscularly or by injection above the formulation's melting temperature. It is believed that a dose of Risperidone of about 4

mg/day is sufficient to prevent psychotic episodes in many patients. Individual variations in tolerance and effectiveness, however, can be wide. Therefore the present invention may be formulated to supply from 1 to 60 mg/day over a period of 1 to 200 days. The advantage of an implanted dosage form is increased compliance, which with psychosis, is a major issue. In one embodiment, at least 50 mg of Risperidone is formulated into a single implantable dosage form by mixing the drug in powdered form with a CYSC polymer at a temperature above the Tm of the polymer, for example, at between 42°C and 60°C. No solvent is required. The mixture is cooled and shaped into solid elongated or approximately spherical implants. In other embodiments, the amount of Risperidone formulated into a single implantable dosage form may be at least 100 mg, or at least 200 mg, or at least 500 mg, or at least 1000 mg, or at least 1500 mg, or at least 2000 mg. In some dosage forms, the total amount of drug may be up to 3, 4 or 5 grams." (p.65, l.17 to p.66, l.4, Paragraph [0238] in the corresponding document)

(I) "The Risperidone implant is introduced subcutaneously into a subject using a trocar. The implant releases Risperidone at an average rate of between 1 and 60 mg (for example no more than 1, 2, 3, 4, 5, 7, 10, 20, 40, 80, 120, 200, or 300 mg) per day over a period of at least 5, 10, 15, 20, 25, 30, 40, 60 or 90 days. In one exemplary embodiment the implant releases Risperidone at an average rate of between 4 and 12 mg per day over a period of at least 7 days. During this period, a desired therapeutic effect is provided for at least 75% of the time. The implant is then removed, or may be left in to erode over time. If a larger bolus of drug is desired, the local area of skin above the implant may be heated by any convenient means." (p.66, l.5-12, Paragraph [0239] in the corresponding document)

4. Comparison with Cited Invention

A. Cited Invention

Cited Document A relates to the field of drug delivery devices and to implantable drug delivery devices made of polyurethane based polymers (3. A. (B)). In Cited Document A, it is stated that to provide polyurethane based long term drug delivery devices and to provide biocompatible and biostable polyurethane based devices for the delivery of drugs or other compounds in a living organism are objects (3. A. (C)).

Cited Document A also discloses drug delivery device for releasing one or more drugs at controlled rates for an extended period of time to produce local or systemic pharmacological effects, having a reservoir having: i) at least one active ingredient; and, optionally, ii) at least one pharmaceutically acceptable carrier; and iii) a polyurethane

based polymer completely surrounding the reservoir and that the reservoir is cylindrically shaped (3. A. (A)).

Furthermore, in Cited Document A, it is stated that a cylindrically shaped reservoir device (cartridge) can be applied, the cartridge can be made with either one end closed or both ends open and the open end can be plugged with pre-manufactured end plug to ensure a smooth end and a solid seal (3. A. (D)) and that to fabricate the cylindrically shaped implants, hollow tubes are produced from a polyurethane, loaded with formulations containing actives and carriers, and the open ends are sealed (3. A. (H) and 3. A. (I)).

If the cylindrically shaped reservoir in Cited Document A is formed into a hollow tube, then the cylindrically shaped reservoir can be considered as a hollow reservoir.

Thus, Cited Document A is considered to describes "drug delivery device for releasing one or more drugs at controlled rates for an extended period of time to produce local or systemic pharmacological effects, having i) at least one active ingredient; and, optionally, ii) at least one pharmaceutically acceptable carrier; and iii) a hollow tube-shaped reservoir having a polyurethane based polymer completely surrounding the reservoir" (hereinafter referred to as "Cited Invention").

B. Comparison with the Invention and Cited Invention

Since the drug delivery device according to Cited Invention releases a drug at a controlled rate for an extended period of time to produce a local or systemic pharmacological effect (3. A. (A), 3. A. (D)), the device is considered to be a drug delivery device for the controlled release of a drug over an extended period of time to produce a local or systemic pharmacological effect.

Moreover, since the drug delivery device according to Cited Invention has an active (a drug) and optionally a carrier filled in a hollow tube shaped reservoir made of a polyurethane based polymer (3. A. (A), 3. A. (H), 3. A. (I)), Cited Invention is considered to comprise a polyurethane-based polymer formed to define a hollow space; and a drug formulation comprising a formulation comprising a drug and optionally one or more pharmaceutically acceptable carriers, wherein the drug formulation is contained in the hollow space.

Furthermore, since the drug delivery device according to Cited Invention can be fabricated as an implant (3. A. (H)) and releases a drug formulation at controlled rates for an extended period of time to produce a local or systemic pharmacological effect (3. A. (A), 3. A. (D)), the drug delivery device is considered to provide a desired release

rate of the drug from the device after implantation.

Thus, in comparison between the Invention and Cited Invention, both are common in the point of

"a drug delivery device for the controlled release of a drug over an extended period of time to produce a local or systemic pharmacological effect, comprising:

a) a polyurethane-based polymer formed to define a hollow space; and

b) a drug formulation comprising a formulation comprising a drug and optionally one or more pharmaceutically acceptable carriers,

wherein the drug formulation is contained in the hollow space,

and wherein the device provides a desired release rate of risperidone from the device after implantation"

and differ in the following points:

* Different feature 1

Whereas the drug is risperidone in the Invention, risperidone is not listed as a drug in Cited Invention.

* Different feature 2

Whereas the drug formulation is a solid drug formulation in the Invention, the drug formulation is not limited to a solid drug formulation in Cited Invention.

5. Judgment

A Regarding the different feature 1

(A) Cited Document B discloses a pharmaceutical formulation comprising a drug and at least one CYSC polymer (3. B. (A)), and also discloses that the CYSC polymer may be a polyurethane (3. B. (B)) and that the drug may be an anti-psychotics and the anti-psychotics may be risperidone (3. B. (C), 3. B. (G), 3. B. (H)). The CYSC polymer stated in Cited Document B is an abbreviation of crystalline side chain polymer and refers to a crystallizable side chain polymer or a crystalline side chain polymer (3. B. (D), 3. B. (E)). Cited Document B discloses that CYSC polymers comprise polymers as illustrated in 3. B. (E) above and a drugs associated with a CYSC polymer can be delivered at controlled rate and/or to a desired location (3. B. (F)).

Thus, the invention stated in Cited Document A and the invention stated in Cited Document B are considered to be in the same technical field of drug delivery systems for releasing a drug at a controlled rate, comprising the drug and a polymer.

(B) As shown in, for example, Japanese Unexamined Patent Application Publication No. S48-040924 Official Gazette, p.3, top left column, l.5-8, p.4, lower

right column, l.16 to p.5, top left column, l.1, p.12, lower right column, l.12-16; National Publication of International Patent Application No. 2004-535431, Paragraphs [0002], [0003], [0024]; and National Publication of International Patent Application No. 2007-517902 Official Gazette, Paragraphs [0001] to [0005], [0065], etc., it is considered to be a common general knowledge before the priority date of the present application that release of antipsychotic (also referred to as a tranquilizer, a tranquilizer.) at a constant rate, that is, a zero-order rate for an extended period of time from an implanted drug delivery system is required.

Thus, it is understood that there is a cause or motivation to have the release of a drug to be used in a drug delivery device at zero-order rate for an extended period of time in Cited Invention, whether the anti-psychotic is hydrophilic or hydrophobic.

Cited Document A also states that the drug (actives) that can be delivered include drugs that can act on the central nervous system, psychic energizers, tranquilizers, and the like (3. A. (F)).

And, since Cited Document B states that risperidone is a psychoactive (antipsychotic) agent (3. B. (G), 3. B. (H)), risperidone is considered to be included in the drugs that can act on the central nervous system or psychic energizers in Cited Document A.

Thus, the invention stated in Cited Document A and the invention stated in Cited Document B are considered to have a similarity in their drugs in that psychoactive agents are applied as drugs.

Furthermore, Cited Document A states that it is an object to control release rate at 0 order to maximize therapeutic effects and minimize unwanted side effects (3. A. (D), Paragraph [0034]). And, Cited Document B states that a continuing problem is obtaining a desired rate of delivery at a desired location and at a desired time (3. B. (D)), and also that they have discovered that useful delivery of drugs can be obtained (3. B. (D)), that the drug may be released with zero-order release kinetics (3. B. (F)), and that the advantage of an implanted dosage form is increased compliance, which with psychosis, is a major issue (3. B. (H)).

Thus, the invention stated in Cited Document A and the invention stated in Cited Document B are considered to have the same object and problem to be solved that are to obtain the zero-order release rate of a drug.

(C) Cited Document B states that the Risperidone implant is introduced

subcutaneously into a subject and that the implant releases Risperidone at an average rate of between 1 and 60 mg (for example no more than 1, 2, 3, 4, 5, 7, 10, 20, 40, 80, 120, 200, or 300 mg) per day over a period of at least 5 days (3. B. (I)). And as stated in (a) above, the invention stated in Cited Document A and the invention stated in Cited Document B are considered to be in the same technical field of drug delivery systems for releasing a drug at a controlled rate, comprising the drug and a polymer. Also, as stated in (B), there is a cause or motivation to release a drug at zero-order rate for an extended period of time in the Cited Invention and the invention stated in Cited Document A and the invention stated in Cited Document B are considered to have the same object and problem to be solved that are to obtain the zero-order release rate of a drug.

Thus, it is what a person skilled in the art can conceive easily to use risperidone as a drug for the purpose of obtaining risperidone-releasing rate at a zero-order rate for an extended period of time in Cited Invention.

(D) The appellant asserts the following in 2. (1) in the written amendment on the statement of the request in the appeal submitted on December 24, 2014.

"Document 2 states that once the polymer and the drug are selected, the permeability coefficient p is constant (Paragraph 0039). However, Document 2 also states that p is a function of the structure of the polymer, the hydrophilicity or hydrophobicity of the polymer, and the interaction with a drug and the polymer (paragraph 0039). Therefore, while it is possible to use the Fick's low to explain the release pattern of a drug once tested, it is not possible to predict the behavior of release until the permeability coefficient is determined. In Document 2, there is no evidence to determine that a delivery is possible in a controlled mode at the therapy level, nor ground to determine how risperidone interacts with a polymer under the influence of the Fick's low. The examiner's decision is based on the descriptions on histrelin, naltrexone and clonidine. However, considering that risperidone is water-insoluble and the other three dissolve in water easily, no sufficient grounds cannot be found in the statement of Documents 2 that similar diffusion behavior is predicted for risperidone." ("Documents 2" is Cited Document A in this Appeal Decision).

Therefore, the statement in Cited Document A is examined. Cited Document A states that the release rate of the drug is governed by the Fick's Law of Diffusion as applied to a cylindrically shaped reservoir device (cartridge) and it is expressed by the

equation illustrated in [Expression 1] (3. A. (D)). The document also states that the permeability coefficient is primarily regulated by the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of drug and the polymer, that once the polymer and the active ingredient are selected, p will be a constant, h, ro, and ri are fixed and kept constant once the cylindrically shaped device is produced, and that Δ C is maintained constant by the carriers inside the reservoir (3. A. (D)).

Based these, since the permeability coefficient p is primarily regulated by the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of drug and the polymer, it is considered that permeability coefficient p can be controlled by regulating the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of drug and the polymer.

According to the aforementioned 3. A. (E), Cited Document A also states that once the cartridges are sealed on both ends with filled reservoir, they are conditioned and primed for an appropriate period of time to ensure a constant delivery rate, that the conditioning and priming step in the process of the preparation of the drug delivery devices is done to obtain a determined rate of release of a specific drug, that while the conditioning and priming step of the implant containing a hydrophilic drug is preferably carried out in an aqueous medium, more preferably in a saline solution, the conditioning and priming step of a drug delivery device comprising a hydrophobic drug is usually carried out in a hydrophobic medium such as an oil based medium, and that the conditioning and priming steps are carried out by controlling three specific factors namely the temperature, the medium and the period of time. And according to the aforementioned 3. A. (E), a hydrophilic drug is preferably conditioned and primed in an aqueous solution and more preferably, in a saline solution, and for example, Histrelin and Naltrexone implants have been conditioned and primed in saline solution, more preferably, conditioned in saline solution of 0.9 % sodium content and primed in saline solution of 1.8% sodium chloride content.

Based on these, since a hydrophilic drug is conditioned and primed in an aqueous solution or a saline solution and Histrelin and Naltrexone implants are conditioned and primed in saline solution, Histrelin and Naltrexone are considered to be hydrophilic drugs. And, since the conditioning and priming step of an implant comprising a hydrophobic drug is usually carried out in a hydrophobic medium such as an oil based medium, it is considered that use of a hydrophobic drug is also intended in Cited Document A.

And, according to the aforementioned 3. A. (G), Cited Document A states that different functional groups can be introduced into the polyurethane polymer chains through the modification of the backbones of polyols depending on the properties desired, that while when the drug delivery device is used for the delivery of water soluble drugs, hydrophilic pendant groups such as ionic, carboxyl, ether, and hydroxy groups are incorporated into the polyols to increase the hydrophilicity of the polymer, when the drug delivery device is used for the delivery of hydrophobic drugs, hydrophobic pendant groups such as alkyl, siloxane groups are incorporated into the polyols to increase the hydrophobicity of the polymer, and that the release rates of the actives (drugs) can also be controlled by the hydrophilicity/hydrophobicity of the polyurethane polymers.

Based on these, It is considered that Cited Document A discloses that when the drug is water-soluble, polyurethane is made hydrophilic and when a drug is hydrophobic, polyurethane is made hydrophobic and also that the release rate of the drug is regulated by doing so.

As appellant points out, Examples in Cited Document A are considered to include Examples when hydrophilic drugs are used. However, since, as stated above, it is considered that use of a hydrophobic drug, but not only hydrophilic drugs, is intended in Cited Document A and the document also discloses that the release rate of a hydrophobic drug is regulated by making the polyurethane polymer hydrophobic, even if Cited Document A discloses only Examples when hydrophilic drugs are used, it is not considered that applications of risperidone, a hydrophobic drug. is excluded.

Also, since it is stated in Cited Document A that the permeability coefficient p can be controlled by regulating the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of the drug and the polymer, it is within the ordinary creativity of the person skilled in the art to optimize these conditions.

Therefore, the aforementioned appellant's allegation cannot be accepted.

B. Regarding the different feature 2

(A) In Examples in Cited Document A, it is stated that pellets of drugs are loaded into tubes (3. A. (J), 3. A. (K)). Pellets are considered to be solid drug formulations.

Thus, formulating an active ingredient and a pharmaceutically acceptable carrier into a solid drug formulation in Cited Invention is only a matter of workshop modification that a person skilled in the art can do as appropriate. And no significant

difficulty is recognized in formulating risperidone and at least one pharmaceutically acceptable carrier into "solid."

(B) The appellant asserts in the written amendment on the statement of the request in the appeal 2. (2) and (3) submitted on December 24, 2014 that Cited Document A does not teach or suggest that a solid formulation of risperidone can be successfully eluted at a zero-order rate through the wall of the polymer and that it is extremely unpredictable for a person skilled in the art whether risperidone can be successfully eluted from various types of drug delivery devices at the time of filling the patent application.

However, as stated in the aforementioned A. (D), since it is stated in Cited Document A that the permeability coefficient p can be controlled by regulating the hydrophilicity/hydrophobicity of the polymer, the structure of the polymer, and the interaction of the drug and the polymer, it is within the ordinary creativity of a person skilled in the art to optimize these conditions. Since it is stated in Cited Document A that it is an object to obtain a zero-order release rate of a drug (3. A. (D), Paragraph [0034]) and the drug release rate of various drugs in various conditions is examined in Examples, it is only a matter of workshop modification that a person skilled in the art can do as appropriate to set conditions so that a solid formulation of risperidone is released at a zero-order rate.

Therefore, the appellant's allegation cannot be accepted.

C. Regarding the effect of the Invention

Paragraph [0003] in the description of the application states "Described herein are methods and compositions based on the unexpected discovery that solid formulations comprising one or more active agents can be used at the core of a polyurethane implantable device such that the active agent is released in a controlled-release, zero-order manner from the implantable device." and indicates that a zero-order release rate of risperidone is obtained according to the Invention.

However, as already stated in the aforementioned A. (B), the invention stated in Cited Document A and the invention stated in Cited Document B are considered to have the same object and problem to be solved that are to obtain the zero-order release rate of a drug. Also, in Examples in Cited Document A, examples exhibiting a stable drug-release rate for an extended period of time is illustrated, as seen in Figures 4-8.

Thus, the effect of the Invention by which the zero-order release rate of risperidone is obtained is not recognized to be a prominent effect that exceeds the

prediction of a person skilled in the art in comparison with the invention stated in Cited Document A and the invention stated in Cited Document B.

D. Summary

Thus, the Invention can be easily invented by a person ordinarily skilled in the art based on inventions stated in Cited Document A and Cited Document B and for which a patent cannot be granted under the provisions of Article 29(2) of the Patent Act.

6. Conclusion

As stated above, the appellant should not be granted a patent for the invention according to Claim 1 of the application under the provisions of Article 29(2) of the Patent Act. Therefore, the application should be rejected without examining inventions according to other claims.

Therefore, the appeal decision shall be made as described in the conclusion.

February 5, 2016

Chief administrative judge:	UCHIDA, Junko
Administrative judge:	YOKOYAMA, Satoshi
Administrative judge:	MAEDA, Kayoko