Patent Right	Date	November 14, 2019	Court	Intellectual Property High Court, Fourth Division
	Case number	2018 (Gyo-Ke) 10110, 10112, 10155		
- A case in which it is not found that the patent right for the invention titled "CELECOXIB COMPOSITION" with a predetermined numeral value range as an invention specifying matter can be recognized such that a person ordinarily skilled in the art could have solved the problem of the invention over the entire predetermined numeral value range from the description in the Detailed Description of the Invention in the Description and common general technical knowledge at the time of the priority date, and the present JPO decision with a conclusion different from that was rescinded due to failure to conform to the "support requirement" prescribed in Article 36, paragraph (6), item (i) of the Patent Act.				

Case type: Patent Act

Result: Partial Rescission of Trial Decision

References: Article 36, paragraph (6), item (i) of the Patent Act

Related rights, etc.: Patent Application No. 2000-584884, Patent No. 3563036, Invalidation Trial No. 2016-800112

Summary of the Judgment

1. The patent application (Patent Application No. 2000-584884) with the international application date of November 30, 1999 (priority date: November 30, 1998 (hereinafter, referred to as the "present priority date"), priority country: U.S.) for the invention titled "CELECOXIB COMPOSITION" was granted registration of establishment of a patent right (Patent No. 3563036, number of claims: 19, hereinafter, this patent is referred to as the "present patent") on June 11, 2004.

   With regard to the present patent, a request for a trial for patent invalidation (Invalidation Trial No. 2016-800112) was made, and the Japan Patent Office dismissed the request for a trial for invalidation for the invention according to Claim 6 deleted by correction and rendered a trial decision that the request for trial for the invention according to the remaining claims is not established (hereinafter, referred to as the "present JPO decision".).

   This case is a case in which plaintiffs sought rescission of the part according to the remaining claims in the present JPO decision excluding Claim 6 for which the request for a trial for invalidation was dismissed.

2. As reasons for rescission of the present JPO decision, Plaintiffs alleged an error in judgment of novelty, an error in judgment of inventive step, an error in judgment of support requirement violation, and an error in judgment of enablement

requirement. This judgment determined that the present JPO decision has an error in the judgment of the support requirement, and rescinded the JPO decision on the part according to the remaining claims excluding Claim 6 for which the request for a trial for invalidation was dismissed, as follows.

3.(1) It is reasonable to determine whether or not the description in the Scope of Claims conforms to the requirement provided for in the item (support requirement) for the invention including a predetermined numeral value range in the invention specifying matter by examining whether it can be recognized that a person ordinarily skilled in the art could solve the problem of the invention over the entire range of the numeral values included in the invention from the description in the Detailed Description of the Invention and the common general technical knowledge at the time of filing.

(2) The invention described in Claim 1 of the Scope of Claims (hereinafter, referred to as "Present Invention 1" and the like) is an invention related to a "pharmaceutical composition containing an orally deliverable solid dosage unit" containing "fine particle celecoxib in a quantity from 10 mg to 1000 mg closely mixed with one or more pharmaceutically acceptable excipient" and is characterized by "having particle size distribution of celecoxib particles D_{90} less than 200 μm in a maximum length of a particle" and thus, it can be considered to be an invention including a predetermined numeral value range in the invention specifying matter.

Then, since it cannot be recognized that a person ordinarily skilled in the art could have solved the problem to provide a pharmaceutical composition containing solid orally deliverable celecoxib particles with improved bioavailability as compared with unblended celecoxib over the entire numeral value range of "celecoxib particle D_{90} less than 200 μm in a maximum length of a particle" included in Present Invention 1 from the description in the Detailed Description of the Invention in the present Description and the common general technical knowledge at the time of the present priority date, it cannot be found to conform to the support requirement.

(3) With regard to the inventions described in Claims 2 to 4 in the Scope of Claims, too, although an upper limit value of the value of the "celecoxib particle D_{90} in the maximum length of the particle" is lower than that of Present Invention 1, it is not found that it can be recognized that a person ordinarily skilled in the art could have solved the problem of Present Invention 1 over the entire numeral value range of the value of the "celecoxib particle D_{90} in the maximum length of the

particle" included in Present Inventions 2 to 4 from the description in the Detailed Description of the Invention in the present Description and the common general technical knowledge at the time of the present priority date similarly to Present Invention 1, and it cannot be found to conform to the support requirement.

(4) The inventions described in Claims 5, 7 to 19 in the Scope of Claims include the pharmaceutical composition described in Claim 1 in the invention specifying matter, but since Present Invention 1 is not found to conform to the support requirement, Present Invention 5 and Present Inventions 7 to 19 cannot be found to conform to the support requirement, either.

Judgment rendered on November 14, 2019
2018 (Gyo-Ke) 10110 A case of seeking rescission of the JPO decision (hereinafter, referred to as the "first case")
2018 (Gyo-Ke) 10112 A case of seeking rescission of the JPO decision (hereinafter, referred to as the "second case")
2018 (Gyo-Ke) 10155 A case of seeking rescission of the JPO decision (hereinafter, referred to as the "third case")
Date of conclusion of oral argument: September 3, 2019

Judgment

First case Plaintiff: Towa Pharmaceutical Co., Ltd. (hereinafter, referred to as "Plaintiff Towa Pharmaceutical")

Second case Plaintiff: Nippon Chemiphar Co., Ltd. (hereinafter, referred to as "Plaintiff Nippon Chemiphar")

Third case Plaintiff: Hexal Aktiengesellschaft (hereinafter, referred to as "Plaintiff Hexal")

First case/Second case/Third case Defendant: G. D. Searle Limited Liability Company (hereinafter, referred to as "Defendant")

Main text

1. In the trial decision made by the Japan Patent Office on June 26, 2018 in the patent invalidation trial case Invalidation Trial No. 2016-800112, parts concerning Claims 1 to 5 and 7 to 19 of Patent No. 3563036 shall be rescinded.
2. Defendant shall bear the court costs.
3. The additional period for filing a final appeal and a petition for acceptance of

final appeal against this judgment shall be 30 days.

Facts and reasons

No. 1 Claims

The same gist as that in the main text, first clause.

No. 2 Outline of the case

1. Outline of procedures at the JPO and the like

(1) Defendant filed a patent application (Patent Application No. 2000-584884. Hereinafter, referred to as the "present application") with the international application date of November 30, 1999 (priority date: November 30, 1998 (hereinafter, referred to as the "present priority date"), priority country: U.S.) for the invention titled "CELECOXIB COMPOSITION" and was granted registration of establishment of a patent right (Patent No. 3563036, number of claims: 19, hereinafter, this patent is referred to as the "present patent") on June 11, 2004 (Exhibits Ko A48, 74).

(2) A. Plaintiff Towa Pharmaceutical made a request for a trial for patent invalidation on the present patent (Invalidation Trial No. 2016-800112, hereinafter, referred to as the "present invalidation trial") on September 30, 2016 (Exhibit Ko A49).

B. Plaintiff Nippon Chemiphar requested participation on the demandant side as a demandant concerning the present invalidation trial pursuant to the provisions in Article 148, paragraph (1) of the Patent Act as of August 3, 2017, and received decision of participation permission as of September 5 of the same year.

Plaintiff Hexal requested participation on the demandant side as a demandant concerning the present invalidation trial pursuant to the provisions in Article 148, paragraph (1) of the Patent Act as of September 25 of the same year, and received decision of participation permission as of November 13 of the same year.

In the present invalidation trial, other than Plaintiff Nippon Chemiphar and Plaintiff Hexal, Nipro Corporation, Nissin Pharmaceutical Co., Ltd., and Ohara Pharmaceutical Co., Ltd. also received participation permission on the demandant side.

(3) Defendant made a request for correction of the Scope of Claims of the present patent as of February 6, 2017 (Exhibit Ko A51) and then, since Defendant received an advance notice of a trial decision as of February 1, 2018 (Exhibit Ko A58), made a request for correction that, with Claims 1 to 19 of the Scope of Claims of the present patent as a group of claims, Claims 1 to 5 and 7 to 19 should

be corrected, and Claim 6 should be deleted (hereinafter, referred to as the "present correction" Exhibit Ko A59) as of May 7 of the same year.

After that, the JPO approved the present correction on June 26 of the same year and made a trial decision stating that "the request for a trial on the invention according to Claim 6 in the Patent No. 3563036 shall be dismissed. The request for a trial on the invention according to Claims 1 to 5 and 7 to 19 in the Patent No. 3563036 is not established." (hereinafter, referred to as the "present JPO decision"), and the certified copy thereof was sent to Plaintiff, Nippon Chemiphar on July 4 of the same year and to Plaintiff Towa Pharmaceutical and Plaintiff Hexal on the 5th day of the same month, respectively.

(4) A. Plaintiff Towa Pharmaceutical instituted the first case lawsuit seeking rescission of the part related to Claims 1 to 5 and 7 to 19 in the present JPO decision on August 2, 2018.

B. Plaintiff Nippon Chemiphar instituted the second case lawsuit seeking rescission of the part related to Claims 1 to 5 and 7 to 19 in the present JPO decision on August 3, 2018.

C. Plaintiff Hexal instituted the third case lawsuit seeking rescission of the part related to Claims 1 to 5 and 7 to 19 in the present JPO decision on November 1, 2018.

2. Description in Scope of Claims

The descriptions in Claims 1 to 5 and 7 to 19 in the Scope of Claims after the present correction are as follows (hereinafter, the invention according to Claim 1 is referred to as "Present Invention 1" and the like in accordance with the claim number, underlined parts are corrections by the present correction, Exhibit Ko A59).

[Claim 1]

A pharmaceutical composition containing fine particle celecoxib in a quantity from 10 mg to 1000 mg closely mixed with one or more pharmacologically acceptable excipients, containing one or more individual solid and orally deliverable dosage units, and having particle size distribution of celecoxib particles D_{90} less than 200 μm in a maximum length of the particle.

[Claim 2]

The pharmaceutical composition according to Claim 1, wherein the celecoxib particles D_{90} are less than 100 μm in a maximum length of the particle.

[Claim 3]

The pharmaceutical composition according to Claim 2, wherein the celecoxib

particles D_{90} are less than 40 μm in a maximum length of the particle.

[Claim 4]

The pharmaceutical composition according to Claim 3, wherein the celecoxib particles D_{90} are less than 25 μm in a maximum length of the particle.

[Claim 5]

The pharmaceutical composition according to Claim 1, characterized by having relative bioavailability at approximately 50% at the minimum of celecoxib as compared with an orally delivered solution containing celecoxib of the same dosage.

[Claim 7]

The pharmaceutical composition according to any one of Claims 1 to 5, wherein the dosage unit is selected from a tablet, a pill, a hard or soft capsule, lozenge, sachet, or pastille.

[Claim 8]

The pharmaceutical composition according to Claim 7, wherein the excipient is in a form of a capsule or a tablet of the unit dosage selected from a pharmaceutically acceptable diluting agent, disintegrating agent, binding agent, humidifying agent, and lubricating agent.

[Claim 9]

The pharmaceutical composition according to Claim 8, characterized by containing:

(a) one or more pharmacologically acceptable diluting agents in a quantity from approximately 10 mass% to approximately 85 mass% of the pharmaceutical composition;

(b) one or more pharmacologically acceptable disintegrating agents in a quantity from approximately 0.2 mass% to approximately 10 mass% of the pharmaceutical composition; and

(c) one or more pharmacologically acceptable binding agents in a quantity from approximately 0.75 mass% to approximately 15 mass% of the pharmaceutical composition;

[Claim 10]

The pharmaceutical composition according to Claim 9, characterized by further containing:

one or more pharmacologically acceptable humidifying agents in a quantity from approximately 0.4 mass% to approximately 10 mass% of the pharmaceutical composition.

[Claim 11]

The pharmaceutical composition according to Claim 9, characterized by further containing:

one or more pharmacologically acceptable lubricating agents in a quantity from approximately 0.2 mass% to approximately 8 mass% of the pharmaceutical composition.

[Claim 12]

The pharmaceutical composition according to Claim 10, characterized by further containing:

one or more pharmacologically acceptable lubricating agents in a quantity from approximately 0.2 mass% to approximately 8 mass% of the pharmaceutical composition.

[Claim 13]

The pharmaceutical composition according to Claim 9, characterized in that

(a) the diluting agent contains lactose; (b) the disintegrating agent contains croscarmellose sodium; and (c) the binding agent contains polyvinylpyrrolidone.

[Claim 14]

The pharmaceutical composition according to Claim 13, characterized by further containing:

a humidifying agent containing sodium lauryl sulfate.

[Claim 15]

The pharmaceutical composition according to Claim 13, characterized by further containing:

a lubricating agent containing magnesium stearate.

[Claim 16]

The pharmaceutical composition according to Claim 13, characterized by further containing:

a humidifying agent containing sodium lauryl sulfate and a lubricating agent containing magnesium stearate.

[Claim 17]

The pharmaceutical composition defined in any one of Claims 1 to 5 and 7 to 16, characterized in that

the pharmaceutical composition is preferably administered orally once or twice a day to a subject in order to treat a symptom or a disease in the subject requiring treatment by cyclooxygenase-2 inhibitor.

[Claim 18]

Use of the pharmaceutical composition defined in any one of Claims 1 to 5 and 7 to 16, for preparation of a drug in a treatment and/or a preventive treatment of a symptom or a disease in a subject requiring treatment by cyclooxygenase-2 inhibitor.

[Claim 19]

Use by Claim 18, wherein the condition or the disease is rheumatoid arthritis, osteoarthritis, or pain.

3 Summary of the present JPO decision

(1) The reason of the present JPO decision is as in the written JPO decision (copy) in the attachment.

The summary is that the clarity requirement violation (invalidation reason I) on Present Inventions 1 to 5 and 7 to 19, enablement requirement violation (invalidation reason II(a) to (c)), and support requirement violation (invalidation reason II(d)), invalidation reasons of lack of novelty of Present Inventions 1, 2, 7, 8, 17 to 19 (invalidation reason III(a)) based on the invention described in the National Publication of International Patent Application No. 1997-506350 gazette (Exhibit Ko A8) which is a publication distributed before the present priority date, lack of novelty of Present Inventions 1, 2, 7, and 18 (invalidation reason III(b)) based on the invention described in the publication distributed before the present priority date, "1997 AAPS ANNUAL MEETING CONTRIBUTED PAPERS ABSTRACTS, front page, publication No. 3469" (Exhibit Ko A15), and lack of inventive step of Present Inventions 1 to 5 and 7 to 19 (invalidation reason IV) with the Exhibit Ko A8 as the primarily cited reference alleged by Plaintiffs have no grounds.

(2) The invention described in the Exhibit Ko A8 (hereinafter, referred to as the "Exhibit Ko 8 Invention) found in the present JPO decision, the difference between Present Invention 1 and the Exhibit Ko 8 Invention, the invention described in the Exhibit Ko A15 (hereinafter, referred to as the "Exhibit Ko 15 Invention"), and the difference between Present Invention 1 and the Exhibit Ko 15 Invention are as follows.

A. Exhibit Ko 8 Invention

"A pharmaceutical composition which is an oral administration unit in a form of a tablet or a capsule in which a celecoxib crystal obtained by the following process 1 and process 2 is combined with one or more auxiliary agents appropriate for an administration path.

Process 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione

4'-methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol

under argon, 12 mL (52.5 mmol) (25%) of sodium methoxide in methanol was added. This mixture was stirred for 5 minutes, and 5.5 mL (46.2 mmol) of ethyl trifluoroacetate was added. After reflux for 24 hours, this mixture was cooled to room temperature and concentrated. To this, 100 mL of 10% HCl was added, and this mixture was extracted by 4 × 75 mL of ethyl acetate. This extract was dried by $MgSO_4$, filtered, and concentrated so as to obtain 8.47 g (94%) of a brown oily substance, and the process proceeded to the next without further refining this.

Process 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

To dione (4.14 g, 18.0 mmol) from the process 1 in 75 mL of dehydrated ethanol, 4.26 g (19.0 mmol) of 4-sulfonamide phenylhydrazine hydrochloride was added. This reactant was made to reflux under argon for 24 hours. This was cooled to room temperature and filtered and then, this reacted mixture was concentrated so as to obtain 6.13 g of an orange solid. This solid was recrystallized from methylene chloride/hexane so as to obtain 3.11 g (8.2 mmol, 46%) of a product as a pale yellow solid."

B. Difference between Present Invention 1 and Exhibit Ko 8 Invention

(Difference 8-1)

The amount of celecoxib contained in the pharmaceutical composition is specified as "a quantity of 10 mg to 1000 mg" in Present Invention 1, while it is not specified in the Exhibit Ko 8 Invention.

(Difference 8-2)

A particle size of celecoxib contained in the pharmaceutical composition is specified as "having distribution of celecoxib particles D_{90} less than 200 μm in a maximum length of the particle" in Present Invention 1, while it is not specified in the Exhibit Ko 8 Invention.

C. Exhibit Ko 15 Invention

"A capsule for oral administration containing 300 mg of celecoxib."

D. Difference between Present Invention 1 and Exhibit Ko 15 Invention

(Difference 15-1)

Celecoxib contained in the pharmaceutical composition is specified as fine particle celecoxib "having distribution of a particle size of celecoxib particles D_{90} less than 200 μm in a maximum length of the particle" in Present Invention 1, while it is not specified in the Exhibit Ko 15 Invention.

(omitted)

No. 4 Judgment of this court

1. Described matters of the present description

(1) The Detailed Description of the Invention in the present description has the following description ([Table 4] (Table 4), [Table 5] (Table 5), [Table 6] (Table 6), [Table 7] (Table 7A), [Table 8] (Table 7B), [Table 12] (Table 11-1), [Table 13] (Table 11-2A), [Table 14] (Table 11-2B), [Table 15] (Table 11-2C), [Table 16] (Table 11-2D), [Table 20] (Table 13-A), [Table 21] (Table 13-B), are as in Attachment 1).

A. [0001]

Field of the Invention

The present invention relates to an orally deliverable pharmaceutical composition containing celecoxib as an active component, a preparation method of the composition, a treatment method of cyclooxygenase-2 mediated disease including oral administration of the composition to a subject, and use of the composition in pharmaceutical manufacture.

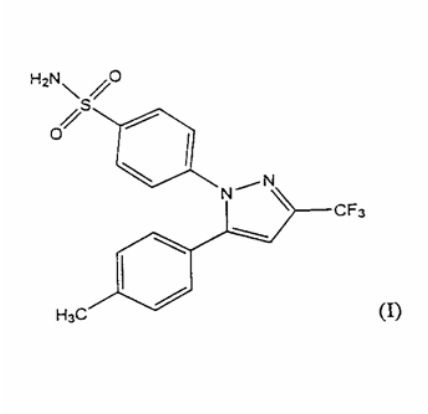
[0002]

Background of the Invention

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (in the present application, hereinafter, referred to as "celecoxib") compound was previously reported in U.S. Patent No. 5,466,823 granted to Talley et al., together with a synthesis method of the compound, explaining the 1,5-diarylpyrazole and the class of salt thereof and described in the Scope of Claims. Celecoxib has the following structure.

[0003]

[Chemical formula 1]



(I)

The 1,5-diarylpyrazole compound reported in U.S. Patent No. 5,466,823 is

described as useful in treatment of inflammation and inflammation-related diseases in this application. U.S. Patent No. 5,466,823 includes an orally deliverable drug amount such as a tablet and a capsule and includes a general standard of dosing formulation of the aforementioned 1,5-diarylpyrazole. U.S. Patent 5,466,823 by Talley et al. describes it as a selective inhibitor of cyclooxygenase-2 and reports the class of 1,5-diarylpyrazole containing celecoxib administered to treat other conditions, diseases, and pathological conditions related to chronic arthritis rheumatism and osteoarthritis.

[0004]

In "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitor: Identification of 4-[5-(4-Methylphenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide (SC-58635, Celecoxib)" by Penning and others in J. Med. Chem. 40 (1997): 1347-1365, a series of syntheses of sulfonamide containing 1,5-diarylpyrazole derivative including celecoxib and evaluation of the derivative as a cyclooxygenase inhibitor are disclosed.

[0005]

In "Preliminary Study of the Safety and Efficacy of SC-58635, a Novel Cyclooxygenase 2 Inhibitor" by Simon et al. in Arthritis & Rheumatism, Vol. 41, No. 9, September 1998, pp. 1591-1602, studies on efficacy and safety of celecoxib in treatment of chronic arthritis rheumatism and osteoarthritis are reported.

[0006]

"Outcome of Specific COX-2 Inhibitor in Rheumatoid Arthritis" by Lipsky et al. in J. Rheumatology, Vol. 24, Suppl. 49, pp. 9-14 (1997) discloses that differential inhibition of cyclooxygenase-2 by celecoxib can sufficiently suppress symptoms and signs of activation of inflammatory diseases in a patient suffering from chronic arthritis rheumatism.

[0007]

European Patent Application No. 0863134A1 published on September 9, 1998 discloses a composition containing a cyclooxygenase-2 inhibitor or more specifically, 2-(3,5-difluorophenyl)-3-(4-methyl-sulfonyl) phenyl"-2-cyclopentene-1-one in combination with a excipient containing microcrystalline cellulose, lactose-hydrate, hydroxypropylcellulose, croscarmellose sodium, and magnesium stearate.

B. [0008]

The formulation of celecoxib for effective oral administration to a subject has been complicated so far due to unique physical and chemical properties of the compound or particularly factors including cohesive power, low bulk density, and low

compressibility related to its low solubility and crystalline structure. Celecoxib is abnormally hardly dissolved in a water-soluble medium. If it is orally administered in a capsule form, for example, since unblended celecoxib is rapidly absorbed in a gastrointestinal tract, it is not easily dissolved or dispersed. In addition, the unblended celecoxib having a crystalline form with a tendency of forming a long and coagulated needle is usually fused at compression on a tablet molding die and becomes a monolithic bulk. When it is blended with another substance, the celecoxib crystal has a tendency of being separated from the other substance, coagulates with celecoxib during mixing of the composition, and becomes a non-uniform blending composition containing an unnecessarily large mass of celecoxib. Therefore, it is difficult to prepare a pharmaceutical component containing celecoxib having desired blending uniformity. Moreover, a problem relating to handling is encountered in preparation of the pharmaceutical component containing celecoxib. For example, it is difficult to handle a small amount required during preparation of a pharmaceutical component, due to the low bulk density of celecoxib. Therefore, there is a need to solve many problems particularly related to preparation of an appropriate pharmaceutical component containing celecoxib in an orally deliverable dose unit and an administration form.

[0009]

In more detail, there is a need of blending of orally deliverable celecoxib having one or more of the following characteristics with respect to the unblended celecoxib or other celecoxib compositions.

(1) Improved solubility
(2) Shorter disintegration time
(3) Shorter dissolution time
(4) Reduced tablet friability
(5) Increased tablet hardness
(6) Improved wettability
(7) Improved compressibility
(8) Improved fluidity of liquid and fine particle solid composition
(9) Improved physical stability of finally finished composition
(10) Decreased tablet or capsule size
(11) Improved blending uniformity
(12) Improved evenness of dosage
(13) Improved control of weight fluctuation in encapsulation and/or making into tablets

(14) Increased granule density of wet-type granular composition
(15) Small quantity of water required for wet-type granulation
(16) Reduced wet-type granulation time
(17) Reduced drying time of wet-type granular mixture

As will be described later, the need of the celecoxib treatment is pointed out in a variety of fields of the cyclooxygenase-2 mediated state and diseases and latently pointed out. Therefore, providing blending in a certain range having specially-made bioavailability characteristics for various adaptations is extremely useful. Providing the blending indicating pharmacokinetics with rapid efficacy is particularly useful in contrast to potentiality with the unblended celecoxib.

[0010]

Such blending would bring about outstanding advance in the treatment of cyclooxygenase-2 mediated state and diseases.

C. [0011]

Summary of the Invention

A pharmaceutical composition containing one or more orally deliverable dosage units is provided, and each unit includes fine particle celecoxib in a quantity of approximately 10 mg to approximately 1000 mg closely mixed with one or more pharmaceutically acceptable excipients.

[0012]

In one working example, there is provided a time path of serum concentration of celecoxib having at least one of the following in one dosage unit when being orally administered to a subject in a fasting state:

(a) Time not longer than approximately 0.5 hours after the administration and reaching 100 ng/ml;
(b) Time not longer than approximately 3 hours after the administration and reaching maximum concentration (T_{max});
(c) Duration for approximately 12 hours or more with the concentration still at 100 ng/ml or more;
(d) Approximately 10 hours or more and a last half-life period ($T_{1/2}$);
(e) Maximum concentration (C_{max}) of approximately 200 ng/ml or more

In another working example, the composition has relative bioavailability of approximately 50% or more as compared with orally delivered solution containing celecoxib in an equal quantity.

[0013]

In still another working example, the composition has distribution of celecoxib

primary particle size so that D_{90} is approximately 200 μm or less (90% of the sample particles is smaller than a D_{90} value) in a longest size of the particle.

[0014]

The dosage unit containing the composition is in individual solid product forms such as a tablet, a pill, a hard or soft capsule, a lozenge, a sachet, or a pastille, or the composition is in a form of a substantially homogenous and fluidable mass such as a fine particle, a granular solid, or a liquid suspension in which one session of a dosage unit is removed to such a degree that measurement is possible.

D. [0017]

Detailed Description of Invention

The novel pharmaceutical composition according to the present invention is an excellent direct-release composition containing one or more orally deliverable dosage units, containing fine particle celecoxib in a quantity of approximately 10 mg to approximately 1000 mg in each dosage unit, and capable of rapid alleviation from cyclooxygenase-2 mediated disease when it is orally administered to a subject suffering from the cyclooxygenase-2 mediated disease.

[0018]

Without being restricted by theories, a great clinical benefit given by the aforementioned composition is considered to be a result of improved bioavailability of celecoxib or particularly astonishingly effective absorption of celecoxib in the gastrointestinal tract. Such effective absorption is understood by a person ordinarily skilled in the art by monitoring the serum concentration of celecoxib of the treated subject over an elapsed time after the administration. It is desirable that a threshold value of the celecoxib concentration in the serum matching effective cyclooxygenase-2 inhibition is reached in as short a time as possible without an acute decrease in the concentration after the administration and the beneficial effect of celecoxib is maintained for as long a time as possible.

[0021]

In an absolute meaning, it is difficult to measure the bioavailability of orally delivered celecoxib. That is because, as it also often happens in celecoxib, venous transport (standard for determination of such bioavailability) has many problems in relation with a drug having low solubility in water. However, the relative bioavailability can be determined in comparison with an orally administered solution of celecoxib in an appropriate solvent. It was found that an astonishingly and relatively high bioavailability can be obtained with the orally delivered composition of the present invention. Thus, in the one working example of the present invention,

each of orally deliverable dosage units, if it is orally administered, has relative bioavailability of approximately 50% or more or preferably 70% or more than the orally delivered solution of celecoxib containing an equal quantity of celecoxib. As will be described later, the bioavailability is derived from comprehensive measurement of the serum concentration of celecoxib over the certain time period after the oral administration.

E. [0022]

The composition of the present invention includes celecoxib in the fine particle form. A primary particle of celecoxib is generated by powdering or crushing or precipitation from a solution, for example, and they are coagulated so as to form a secondary aggregate particle. The term "particle size" used in this application refers to a longest size of the primary particle unless otherwise particularly pointed out in this application. The particle size is considered to be an important parameter influencing the clinical effect of celecoxib. Thus, in another working example, the composition of the invention has particle distribution of celecoxib so that particle D_{90} is approximately 200 μm or less, preferably approximately 100 μm or less, more preferably approximately 75 μm or less, further preferably approximately 40 μm or less, most preferably approximately 25 μm or less in a particle maximum length. Usually, the bioavailability of celecoxib is improved by a reduction in the particle size of celecoxib according to the aforementioned working example of the present invention.

[0023]

In addition, the celecoxib particle in the composition of the present invention preferably has an average particle size of approximately 1 μm to approximately 10 μm or particularly preferably approximately 5 μm to approximately 7 μm.

[0024]

Making the composition of the present invention by crushing celecoxib by an impact-type mill such as a pin mill prior to mixing of celecoxib and the excipient was found to be not only effective in providing the improved bioavailability but also useful in overcoming the problems in relation with cohesive characteristics of the celecoxib crystal during such mixing or blending. The celecoxib crushed by using the pin mill has a cohesive power smaller than that of uncrushed celecoxib or celecoxib crushed by using other types of mills such as a liquid energy mill, and does not coagulate easily to the secondary aggregate of the celecoxib particles during blending. A degree of blending evenness becomes high by the decreased cohesive power, and this is extremely important in blending in a unit dosage form such as a

capsule and a tablet. This brings about an unexpected result in usability of the liquid energy mill such as an air jet mill when other pharmaceutical compounds for blending are blended. Without being restricted by a specific theory, the crystalline form of celecoxib is altered by the impact crushing from a long needle state to a more even crystal form and becomes more appropriate for the blending purpose, but it is assumed that the long needle-state crystal tends to remain in the air jet mill.

[0025]

It was also found that the blend uniformity is further improved by subjecting celecoxib to wet-type granularization with a carrier material so as to prepare a pharmaceutical component, particularly when celecoxib used as a starting material is crushed by an impact mill. It is particularly desirable that the celecoxib starting material is subjected to impact crushing so as to have the aforementioned particle size and then, to the wet-type granularization.

[0026]

In another working example, the new pharmaceutical composition of the present invention contains celecoxib together with one or more carrier materials or excipients selected from a diluting agent, a disintegrating agent, a binding agent, a humidifying agent, and a lubricating agent. The at least one carrier material is preferably a water-soluble diluting agent or a humidifying agent. Such water-soluble diluting agent or humidifying agent promotes dispersion and dissolution of celecoxib when the pharmaceutical composition is taken in. Both the water-soluble diluting agent and humidifying agent are preferably present. The component of the present invention is substantially uniform and a fluidable mass such as a fine particle, a granular solid, or a liquid, and assumes a form of an individual article such as a capsule or a tablet including one session of dosage unit.

F. [0028]

Usefulness of composition of the invention

The composition of the present invention is effective for treatment and prevention of a wide range of diseases mediated by cyclooxygenase-2. The currently considered composition is useful for treatment of inflammation of a subject as, although not limited to the following, analgesic drugs in treatment of pain and headache, and antipyretics in treatment of a fever, for example. The composition is useful for, although not limited to the following, treatment of joint diseases including chronic arthritis rheumatism, marrow arthritis, gout arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis, for example. Moreover, the composition is useful for treatment of asthma, bronchitis, menstrual colic, pre term labor, tendinitis,

bursitis, allergic neuritis, cytomegalovirus infection, apoptosis including HIV induced apoptosis, lower back pain, hepatic diseases including hepatitis, skin related states such as psoriasis, eczema, acne, UV damage, burn, and dermatitis, postoperative inflammations after an operation including ophthalmic operation, such as after surgeries of cataract or a refractive surgery. The considered composition is useful for treatment of gastrointestinal conditions such as diseases related to inflammatory bowel diseases, Crohn disease, gastritis, irritable bowel syndromes, and ulcerous colitis. The considered composition is useful for treatment of inflammations in diseases such as migraine, periarteritis nodosa, thyroiditis, anaplastic anemia, Hodgkin disease, sclerodoma, rheumatism fever, type 1 diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling after injury including brain edema, and myocardial ischemia. The considered composition is useful for treatment of ocular diseases such as retinitis, conjunctivitis, retinopathy, uveitis, and ocular photophobia and acute injury to ocular tissues. The considered composition is useful for treatment of pneumonia related to viral infection and cystic fibrosis and bone resorption related to osteoporosis. The considered composition is useful for treatment of specific central nerve system diseases such as cortical dementia including Alzheimer's disease and neuronal degeneration and central nerve system injury as the result of a seizure, ischemia, and trauma. The term "treatment" used in the present application includes partial or complete suppression of dementia including Alzheimer's disease, vascular dementia, multiple infarct dementia, presenile dementia, alcohol amnestic disorder, and senile dementia.

G. [0039]

Definitions

The term "active component" used in the present application means celecoxib unless particularly noted otherwise.

[0040]

The term "excipient" used in the present application refers to a substance used as a vehicle for transporting the active component to a subject, and a substance added to the active component improves handling or enables formation of the composition generated as the result in a desired and consistent orally deliverable unit dosage, for example. The excipients include, but are not limited to, a diluting agent, a disintegrator, a binding agent, an adhesive, a humidifying agent, a lubricating agent, a glidant, and a substance added for masking, a substance added for cancelling a bad

taste or odor and improving the flavor, a coloring matter, an appearance of administration form, and substances other than the active component having been used for preparation of the oral administration form.

[0041]

The term "adjuvant" used in the present application refers to those improving an action of the active component present in the pharmaceutical component containing the active component or when it is added. The term "unit dosage" used in the present application refers to a quantity of the active component intended for one session of oral administration to the subject for treatment or prevention of the cyclooxygenase-2 mediated state or diseases. The treatment of the cyclooxygenase-2 mediated disease required regular unit administration of celecoxib, and one session of unit administration is twice or more a day, the one session of unit administration is performed at each meal, the one session of unit administration is performed every four hours or other intervals, and it may be once a day, for example.

The term "dosage unit" used in the present application refers to a part of the pharmaceutical composition containing the one session of unit dosage of the active component. In the object of the present invention, the dosage unit is a form of individual articles such as a tablet or a capsule and has a measurable volume such as a solution, a suspension, and the like containing the unit dosage of the active component.

[0042]

The term "orally deliverable" used in the present application means administration to a gastrointestinal tract of the subject through the mouth of the subject.

[0043]

The term "substantially homogenous", used in the present application in order to explain the pharmaceutical composition containing a combination of the components, means that the components are sufficiently mixed, and the individual components are not separated into individual layers or concentration gradient does not occur in the components.

[0044]

The term "bioavailability" used in the present application is related to a scale of the quantity of the active component absorbed in a blood flow through the gastrointestinal tract. More specifically, the "bioavailability" used in the present application is expressed by $AUC_{(0-\infty)}$ and particularly expressed by the orally delivered component, expressed as a ratio of $AUC_{(0-\infty)}$ to the active component in the same dosage delivered through the vein.

[0045]

The term "relative bioavailability" in the present application is expressed by $AUC_{(0-\infty)}$ of the specific orally administered component expressed as a ratio of $AUC_{(0-\infty)}$ to the solution of the active component orally administered in the same dosage.

[0046]

The terms "$AUC_{(0-24)}$", "$AUC_{(0-48)}$", and "$AUC_{(0-72)}$" in the present application mean an area under a curve determined by the linear trapezoidal rule, expressed by the unit of (ng/ml)h, and related to the serum concentration at 24 hours, 48 hours, or 72 hours from 0 after administration, respectively.

[0047]

The term "$AUC_{(0-LQC)}$" means an area under a curve determined by the linear trapezoidal rule, expressed by the unit of (ng/ml)h, and related to the serum concentration at time of last quantified concentration ("LQC") from 0 after the administration. The term "$AUC_{(0-\infty)}$" in the present application is calculated as $AUC_{(0-LQC)}$ + LQC / (-b), where LQC is the last quantified serum concentration, and b is inclination from the calculation of $T_{1/2}$, and is expressed by the unit of (ng/ml)h.

[0048]

The term "C_{max}" in the present application means the maximum serum concentration calculated or estimated from the observed maximum serum concentration or the concentration/time curve and expressed by the unit of ng/ml. The term "T_{max}" in the present application means the time when "C_{max}" is reached after the administration and is expressed by the unit of time (h).

[0049]

The term "$T_{1/2}$" in the present application means the last half-life period of the serum concentration to a data point at the final stage of the concentration-time curve, determined from a simple linear regression of natural logarithm log (ln) concentration to time. $T_{1/2}$ is calculated as -ln (2) / (-b) and expressed by the unit of time (h).

[0050]

The term "absorption speed" in the present application means C_{max} / $AUC_{(0-LQC)}$.

H. [0051]

<u>Celecoxib administration provided by the composition of the present invention</u>

The pharmaceutical composition of the present invention is suitable for administration of celecoxib in the dosage per day from approximately 10 mg to approximately 1000 mg. Usually, each of the dosage unit of the composition of the present invention includes the quantity of celecoxib in the dosage of one day from

one-tenth to the whole of the dosage of one day. The composition of the present invention contains celecoxib in the quantity from approximately 10 mg to approximately 1000 mg, preferably from approximately 50 mg to approximately 800 mg, more preferably from 75 mg to approximately 400 mg, and further preferably from approximately 100 mg to approximately 200 mg for the dosage unit. When the dosage unit is in the form of the individual articles suitable for oral administration or when it is a capsule or a tablet, for example, each of such articles contains celecoxib in a quantity from approximately 10 mg to approximately 1000 mg, preferably from approximately 50 mg to approximately 800 mg, more preferably from approximately 75 mg to approximately 400 mg or further preferably from approximately 100 mg to 200 mg.

[0054]

Treatment of specific state and disease

The pharmaceutical composition of the present invention is useful when administration of the cyclooxygenase-2 inhibitor is needed. The aforementioned composition is effective for treatment of rheumatoid arthritis and osteoarthritis; for example, control of pains in general (pains after specific oral surgical operations, pains after general surgeries, pains after plastic surgeries, and acute expansion of osteoarthritis) and particularly for treatment of Alzheimer's disease and chemical prevention of colonic cancer.

[0055]

In the treatment of rheumatoid arthritis, the composition of the present invention can be used for the daily dosage of celecoxib in the quantity from approximately 50 mg to approximately 1000 mg, preferably from approximately 100 mg to approximately 600 mg, more preferably from approximately 150 mg to approximately 500 mg, or further preferably from approximately 175 mg to approximately 400 mg, or of 200 mg, for example. When the composition of the present invention is administered, the daily dosage of celecoxib in the quantity from approximately 0.67 to 13.3 mg per body weight, preferably from approximately 1.33 to approximately 8.00 mg per body weight, more preferably from approximately 2.00 to approximately 6.67 mg per body weight or further preferably from approximately 2.33 to approximately 5.33 mg per body weight, or approximately 2.67 mg per body weight, for example, is usually appropriate. Regarding the number of sessions of administration per day, once to four times per day or preferably once or twice of administration per day is preferable. It is preferable to administer the composition of the present invention at the rate of 100 mg per session and twice a day for many patients, but the dosage of

200 mg per session and twice a day or two sessions of administration of 100 mg per session can be useful for some patients.

[0056]

In the treatment of osteoarthritis, the composition of the present invention can be used for providing a dosage of celecoxib for a day from approximately 50 mg to approximately 1000 mg, preferably from approximately 100 mg to approximately 600 mg, more preferably from approximately 150 mg to approximately 500 mg, further preferably from approximately 175 mg to approximately 400 mg or approximately 200 mg, for example. When the composition of the present invention is to be administered, a dosage of celecoxib for a day from approximately 0.67 mg to approximately 13.3 mg per kg body weight, preferably from approximately 1.33 to approximately 8.00 mg per kg body weight, more preferably from approximately 2.00 mg to approximately 6.67 mg per kg body weight, further preferably from approximately 2.33 to approximately 5.33 mg per kg body weight or approximately 2.67 mg per kg body weight, for example, is usually appropriate. The number of administration sessions a day is once to four times a day or preferably once or twice of administration a day is preferable. The composition of the present invention is preferably administered at a rate of 100 mg per session for twice of administration a day or 200 mg per session for once of administration a day.

I. [0062]

Form of composition of the present invention

The pharmaceutical composition of the present invention includes celecoxib combined with one or more preferable non-toxic and pharmaceutically acceptable carriers, excipient, and adjuvant (in the present application, they are collectively called a "carrier material" or a "excipient") which are suitable for oral administration. The carrier material should be accepted in the meaning that it has compatibility with other components of the composition and moreover, it should not be harmful for the excipient. The composition of the present invention is suitable to be administered via an appropriate oral route by selection of an appropriate carrier material and the dosage of celecoxib which is effective for the intended treatment. Therefore, the carrier material to be used is solid or liquid or both, and the composition contains celecoxib from approximately 1% to approximately 95%, preferably from approximately 10% to approximately 90%, more preferably from approximately 25% to approximately 85% or further preferably from approximately 30% to approximately 80% in weight. The pharmaceutical composition of the present invention includes mixing of the components and can be prepared by the art related to any one of arts

related to well-known pharmacology.

[0067]

Carrier material or excipient

As described above, the pharmaceutical composition of the present invention includes celecoxib in a quantity per dosage unit effective for treatment or preventive treatment in combination with one or more pharmaceutically acceptable carrier materials suitable for oral administration. The composition of the present invention preferably includes a desired quantity of celecoxib mixed with one or more carrier materials selected from a group consisting of a pharmaceutically acceptable diluting agent, disintegrating agent, binding agent, adhesive, humidifying agent, lubricating agent, and anti-adhesive. More preferably, the composition is in the form of an immediately released capsule or tablet and is made tablet or encapsulated for conventional administration.

[0068]

By selection and combination of the carrier materials to be used in the pharmaceutical composition of the present invention, the composition indicates improved performances in relation with efficacy, bioavailability, clearance time, stability, compatibility between celecoxib and the carrier material, safety, dissolution profile, disintegration profile, and/or other pharmacokinetic, chemical, and/or physical properties. The carrier material is preferably water-soluble or water-dispersible and has a wettability property offsetting low aqueous solution solubility and hydrophobicity of celecoxib. When the composition is blended as a tablet, the dissolution and disintegration profiles, hardness, crush strength, and/or crushability are improved by the combination of the selected carrier material.

[0069]

Diluting agent

The pharmaceutical composition of the present invention arbitrarily includes one or more pharmaceutically acceptable diluting agents as a carrier material. The appropriate diluting agents are used individually or in combination and include lactose USP; lactose USP anhydride; lactose USP spray drying; starch USP; directly compressed starch; mannitol USP; sorbitol; dextrose monohydride; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluting agent; powdered sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granule NF; dextrate, NF (Emdex, for example); Celutab; Dextrose (Cerelose, for example); inositol; hydrolyzed cereal such as Maltron and Mor-Rex; amylose; Rexcel; powder cellulose (Elcema, for example);

calcium carbonate; glycine; bentonite; polyvinyl pyrrolidone and the like. If present, such diluting agent as a whole is preferably contained from approximately 5% to approximately 99%, preferably from approximately 10% to approximately 85%, or more preferably from approximately 20% to approximately 80% to the total weight of the composition. The selected diluting agent or diluting agents preferably present appropriate fluidity and compressibility if tablets are preferable.

[0070]

Lactose and microcrystalline cellulose used singularly or in combination are preferable as diluting agents. Both diluting agents have chemical compatibility with celecoxib. By using extra-granular microcrystalline cellulose (that is, microcrystalline cellulose is added to the wet-type granular composition after the drying process), hardness and/or disintegration time (of the tablet) is improved. Lactose, or more specifically, lactose monohydride, is particularly preferable. Usually, lactose provides the pharmaceutical composition having an appropriate celecoxib emission speed, stability, fluidity for prior compression, and/or drying property with a relatively low diluting agent cost. (If the wet-type granular is used) a substance with high density promoting higher density in the granulation is provided and thus, blend fluidity is improved.

[0071]

Disintegrating agent

The pharmaceutical composition of the present invention arbitrarily includes one or more pharmaceutically acceptable disintegrating agents as a carrier material particularly for tablet formulation. Appropriate disintegrating agents used singularly or in combination include starch; starch sodium glycolate; clays (such as Veegum HV); cellulose (such as refined cellulose, methyl cellulose, carboxymethylcellulose sodium, and carboxymethylcellulose); alginic acids; cornstarch gelatinized in advance (such as National 1551 and National 1550); crospovidone USP NF; and rubber (such as agar, guar, locust bean, Karaya, pectin, and Tragacanth). The disintegrating agent can be added in an appropriate process during preparation of the pharmaceutical composition or particularly preferably during a lubrication process before granulation or before compression. If present, the disintegrating agent as a whole includes the quantity from approximately 0.2% to approximately 30%, preferably from approximately 0.2% to approximately 10%, or more preferably from approximately 0.2% to approximately 5% to the total weight of the composition.

[0072]

Croscarmellose sodium is a preferable disintegrating agent as a tablet or

capsule disintegrating agent and if present, it includes the quantity from approximately 0.2% to approximately 10%, preferably from approximately 0.2% to approximately 6%, or more preferably from approximately 0.2% to approximately 5% to the total weight of the composition. Excellent in-granular disintegration capability is given to the composition of the present invention by croscarmellose sodium.

[0073]

Binding agent and adhesive

The composition of the present invention arbitrarily includes one or more pharmaceutically acceptable binding agents or adhesives as a carrier material particularly for tablet formulation. It is preferable that a sufficient cohesive power is applied to a powder to be made tablet so that usual treatment such as sizing, lubrication, compression, and packaging is made possible by the binding agent and the adhesive, and the tablet is capable of disintegration, and the composition is absorbed by intake. Appropriate binding agents and adhesives used singularly or in combination include gum Arabic; Tragacanth; sucrose; gelatin; glucose; starch; although not limited to the following, cellulose materials such as methylcellulose and sodium carboxymethylcellulose (Tylose, for example); alginic acids and salts thereof; aluminum magnesium silicate; polyethylene glycol; guar gum; polysaccharide acids; bentonite; polyvinylpyrrolidone; polymethacrylate; hydroxypropyl methylcellulose (HPMC); hydroxypropyl cellulose (Klucel); ethyl cellulose (Ethocei); and starches gelatinized in advance (such as National 1511 and Starch 1500). If present, the binding agent and/or adhesive include a quantity of all the binding agents and/or adhesives from approximately 0.5% to approximately 25%, preferably from approximately 0.75% to approximately 15%, or more preferably from approximately 1% to approximately 10% to the total weight of the composition.

[0074]

Polyvinylpyrrolidone is a preferable binding agent used for applying cohesiveness to celecoxib powder blend and other excipients for granulation of celecoxib blending. If present, polyvinylpyrrolidone includes a quantity from approximately 0.5% to approximately 10%, preferably from approximately 0.5% to approximately 7%, or more preferably from approximately 0.5% to approximately 5% to the total weight of the composition. Polyvinylpyrrolidone with viscosity up to approximately 20 cPs is used, but viscosity of approximately 6 cPs or less is preferable and approximately 3 cPs or less is particularly preferable. The cohesive power is applied to the powder blend by polyvinylpyrrolidone, required binding occurs easily, and granules are

formed during the wet-type granulation. In addition, the composition of the present invention including polyvinylpyrrolidone is prepared particularly by wet-type granulation and it was found to indicate relatively improved bioavailability over the other compositions.

[0075]

Humidifying agent

Celecoxib is not dissolved in an aqueous solution easily. Therefore, the pharmaceutical composition of the present invention arbitrarily but preferably includes one or more pharmaceutically acceptable humidifying agents as a carrier material. The humidifying agent is preferably selected so that celecoxib maintains affinity with water, and that state is considered to improve the relative bioavailability of the pharmaceutical composition. Appropriate humidifying agents used singularly or in combination include oleic acid; glyceryl monostearate; sorbitan monooleic acid ester; sorbitan monolauric acid ester; triethanolamine oleate; polyoxyethylene sorbitan monooleic acid ester; polyoxyethylene sorbitan monolauric acid ester; sodium oleate; and sodium lauryl sulfate. The humidifying agents which are anionic surfactants are preferable. If present, the humidifying agents include a quantity as all the humidifying agents from approximately 0.25% to approximately 15%, preferably from approximately 0.4% to approximately 10%, or more preferably from approximately 0.5% to approximately 5% to the total weight of the composition.

[0076]

Sodium lauryl sulfate is a preferable humidifying agent. If present, sodium lauryl sulfate is contained in a quantity from approximately 0.25% to approximately 7%, preferably from approximately 0.4% to approximately 6%, or more preferably from approximately 0.5% to approximately 5% to the total weight of the composition.

[0077]

Lubricating agent

The pharmaceutical composition of the present invention arbitrarily includes one or more pharmaceutically acceptable lubricating agent and/or glidant as a carrier material. Appropriate lubricating agents and/or glidants used singularly or in combination include glyceryl behapate (Compritol 888); stearates (magnesium, calcium, and sodium) stearic acid, hydrogenated vegetable oils; (Sterotex, for example); talc; wax; Stearowet; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; polyethylene glycol (carbowax 4000 and carbowax 6000, for example); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. If present, the lubricating agent as a whole includes a quantity from

approximately 0.1% to approximately 10%, preferably from approximately 0.2% to approximately 8%, or more preferably from approximately 0.25% to approximately 5% to the total weight of the composition.

Magnesium stearate is a preferable lubricating agent and is used for reducing friction between a device during compression for tablet formulation and granulated mixture, for example. Other carrier materials (such as anti-adhesive, a coloring agent, a flavoring agent, a sweetener, and a preservative) are well known in the field of the pharmaceutical arts and can be contained in the composition of the present invention. For example, iron oxide may be added to the composition to turn the color to yellow.

[0078]

Capsule and tablet

In a working example of the present invention, the pharmaceutical composition is in the form of a capsule and a tablet of a unit dosage and contains a desired quantity of celecoxib and a binding agent. The preferable composition further contains one or more carrier materials selected from a group consisting of pharmaceutically acceptable diluting agent, disintegrating agent, binding agent, humidifying agent, and lubricating agent. More preferably, the composition contains one or more carrier materials selected from a group consisting of lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Further preferably, the composition contains lactose monohydrate and croscarmellose sodium. Further preferably, the composition further contains one or more carrier materials, that is, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose.

J. [0124]

Particle size of celecoxib in capsule and tablet

It was found that bioavailability of celecoxib is improved by reduction in the celecoxib particle size when it is orally administered in the form of a capsule or a tablet. Therefore, the celecoxib D_{90} particle size is approximately 200 μm or less, preferably approximately 100 μm or less, more preferably approximately 75 μm or less, further preferably approximately 40 μm or less, or most preferably approximately 25 μm or less. As exemplified in Example 11, for example, by reducing the celecoxib D_{90} particle size as a start material from approximately 60 μm to approximately 30 μm, the bioavailability of the composition is extremely improved. In addition or alternatively, celecoxib has an average particle size within a range from approximately 1 μm to approximately 10 μm or preferably from approximately 5 μm

to approximately 7 μm.

[0125]

Granulated secondary particle size and fluidity

The pharmaceutical composition of the present invention can be prepared by direct encapsulation or direct compression, for example, but it is preferable that it is granulated in wet type prior to encapsulation or compression. Wet-type granulation increases the density of crushed composition, improves fluidity and compression characteristics among other effects, and makes measurement or weight dispersion of the composition easier in encapsulation or making it tablets. The secondary particle size generated from the granulation (that is, the granule size) is not important in strict meaning, but an average granule size is important in enabling conventional handing and working of making tablet so that the directly compressible mixture forming a pharmaceutically acceptable tablet can be generated.

K. [0134]

Preparation method of celecoxib composition

The present invention also relates to a preparation method of a pharmaceutical composition containing celecoxib. Particularly, the present invention relates to a preparation method of the pharmaceutical composition containing celecoxib in a fine particle form. More specifically, the present invention relates to a preparation method of the celecoxib composition in a tablet or capsule form in separate unit dosage, and each of the tablets or capsules contains a sufficient quantity of celecoxib in a quantity to realize a treatment effect over approximately 12 to 24 hours. For example, each dosage unit preferably contains celecoxib in a quantity from approximately 100 mg to approximately 200 mg. According to the present invention, the tablet or capsule composition of the present invention is prepared by using wet-type granulation, dry-type granulation, or a direct compression or encapsulation method.

[0135]

Wet-type granulation is a preferable preparation method of the pharmaceutical composition of the present invention. In the wet-type granulation process, celecoxib is first crushed or pulverized to a desired particle size (together with one or more carrier materials, if necessary). Various mills or crushers can be used, but by using impact crushing such as pin milling of celecoxib, improved blending uniformity can be realized in the final composition as compared with other types of crushing. For example, to cool celecoxib by using liquid nitrogen is needed during crushing in order to avoid heating of celecoxib to an unnecessary temperature. As described above, it

is important to reduce the D_{90} particle size to approximately 200 μm or less, preferably to approximately 100 μm or less, more preferably to approximately 75 μm or less, further preferably to approximately 40 μm or less, or most preferably to approximately 25 μm or less during the aforementioned crushing process for the bioavailability of celecoxib to increase.

[0136]

The crushed or finely crushed celecoxib is blended with one or more carrier materials including a carrier material crushed with celecoxib by a high shear mixer/granulator, a planetary mixer, a twin-shell type blender, or a sigma mixer, for example, so as to generate a dry-powder mixture. Typically, a drug is blended with one or more diluting agents, disintegrating agents, and/or binding agents and selectively with one or more humidifying agents in the aforementioned process, and one or more carrier materials are added to all or a portion in the subsequent process. For example, it was found that, in the tablet preparation in which croscarmellose sodium is used as the disintegrating agent, disintegration of the manufactured tablet is improved by addition of croscarmellose at a portion during the blending process (generating croscarmellose sodium in a granule) and addition of the remaining portion after the drying process which will be described later (generating croscarmellose sodium outside the granule). In the situation, approximately 60% to approximately 75% of croscarmellose sodium is added into the granule, while approximately 25% to approximately 40% of croscarmellose sodium is added to outside the granule. Similarly, in the tablet preparation, it was found that compressibility of the granule is improved by addition of the microcrystalline cellulose (generating microcrystalline cellulose outside the granule) after the following drying process, and hardness of the tablet prepared from the granule is also improved.

[0137]

The aforementioned blending process includes blending of celecoxib, lactose, polyvinyl pyrrolidone, and croscarmellose sodium. It was found that a dry powder mixture of celecoxib having sufficiently uniform dispersion is generated in as short a blending time as approximately 3 minutes. For example, the dry powder mixture used for preparation of a 100-mg dosage capsule (all the batch sizes of 1080 Kg) and a 200-mg dosage capsule (all the batch sizes of 918 Kg) has celecoxib concentration indicating measured relative standard deviation values of 3.6% or less and 1.1% or less, respectively.

[0138]

After that, water or preferably purified water is added to the dried powder mixture,

and the mixture is blended for additional time so as to generate a wet granular mixture. The humidifying agent is preferably used, and first, water is added, and prior to addition of the water to the dried powder mixture, mixing is performed at least for 15 minutes or preferably for 20 minutes. Water can be immediately added to the mixture, gradually added by taking time, or added in several times by taking time. Preferably, water is added gradually. Alternatively, the humidifying agent is added to the dried powder mixture, and then water can be added to the mixture generated as the result.

[0139]

For example, in the case of an exemplified 100 mg of dosage capsule (1080 Kg batch), a water adding speed is approximately 5 to approximately 25 kg/min, preferably approximately 7 to approximately 20 kg/min, or more preferably approximately 8 to approximately 18 kg/min, which gives an appropriate result. The further mixing time after addition of water is finished is preferably such time that ensures uniform dispersion of water in the mixture. The aforementioned exemplified mixing time of addition in a batch is from approximately 2 to approximately 10 minutes, preferably from approximately 3 to approximately 9 minutes, more preferably from approximately 3 to approximately 7 minutes, which gives an appropriate result. The wet granular mixture of the aforementioned batch contains water in approximately 2 weight% to approximately 15 weight%, preferably approximately 4 weight% to approximately 12 weight%, or more preferably approximately 6 weight% to approximately 10 weight%.

[0140]

For example, in the case of an exemplified 200 mg of dosage capsule (918 Kg batch), a water adding speed is approximately 5 to approximately 25 kg/min, preferably approximately 7 to approximately 23 kg/min, or more preferably approximately 8 to approximately 21 kg/min, which gives an appropriate result. The further mixing time after addition of water is finished is preferably such time that ensures uniform dispersion of water in the mixture. The aforementioned exemplified further mixing time of addition in a batch is from approximately 2 to approximately 15 minutes, preferably from approximately 3 to approximately 12 minutes, more preferably from approximately 3 minutes to approximately 10 minutes, which gives an appropriate result. The wet granular mixture of the aforementioned batch contains water in approximately 2 weight% to approximately 15 weight%, preferably approximately 6 weight% to approximately 14 weight%, or more preferably approximately 8 weight% to approximately 13 weight%.

[0141]

After that, the wet granular mixture is crushed in a wet type by a screening mill, for example, and excludes large aggregate of the materials generated as byproducts in the wet-type granulation process. If the aggregates cannot be removed, the aggregate prolongs time of the subsequent fluid bed drying process, and fluctuation factors in relation with moisture control are increased. In the exemplified 100-mg dosage capsule (1080 Kg batch) and the 200-mg dosage capsule (918 Kg batch), appropriate granules are obtained by using the feed rate of approximately 50% of a maximum feed rate, preferably from approximately 2% to approximately 30%, or more preferably from approximately 5% to approximately 20%, for example.

[0142]

Then, the mixture subjected to wet-type granulation or crushed in the wet type is dried in an oven or a fluid-bed drier or preferably a fluid-bed drier so as to generate dried granules. If necessary, the wet-type granulated mixture is pushed out and made spherical prior to the drying. In the drying process, the conditions such as a temperature of an inlet air and drying time are adjusted so as to obtain a desired moisture content of the dried granule. In the aforementioned drying process and the subsequent treatment process, two or more granulation sections are preferably combined.

[0143]

In the aforementioned exemplified 100-mg dosage capsule (1080 kg batch) or 200-mg dosage capsule (918 kg batch), the inlet temperature of the drier is fixed to 60°C, but other inlet temperatures are preferably used within a range from approximately 50°C to approximately 70°C. Air airflow speed is, at a damper opening portion from approximately 10% to approximately 90%, preferably from approximately 20% to approximately 80% or more preferably from approximately 30% to approximately 70%, changed within a range from approximately 1000 to 8000 cubic feet/min, preferably from approximately 2000 to approximately 7000 cubic feet/min, or more preferably from approximately 4000 to approximately 7000 cubic feet/min. A drier load from approximately 35% to approximately 100%, preferably from approximately 50% to approximately 100%, or more preferably from approximately 90% to approximately 100% is used. An average loss in drying of the dried granule adjusted under the aforementioned conditions is usually approximately 0.1 weight% to approximately 2.0 weight%.

[0144]

After that, the size of the dried granules is made smaller to a required degree in

preparation by compression or encapsulation. Conventionally publicly-known particle size reducing devices such as an oscillator or an impact-type mill (such as Fitz mill) can be used. In the exemplified 100-mg dosage capsule (1080 kg batch), an appropriate granule size reduction can be obtained by using a feed rate from approximately 20% to approximately 70% or preferably from approximately 30% to approximately 60%, a mill speed from approximately 20% to approximately 70% or preferably from approximately 40% to approximately 60%, and a screen size from approximately 0.020 inches (0.5 mm) to approximately 0.070 inches (1.7 mm) or preferably from approximately 0.028 inches (0.7 mm) to approximately 0.040 inches (1.0 mm). In the exemplified 200-mg dosage capsule (918 kg batch), appropriate granulation can be performed by using the feed rate from approximately 10% to approximately 70% or preferably from approximately 20% to approximately 60%, the mill speed from approximately 20% to approximately 60% or preferably from approximately 30% to approximately 50%, and a screen size from approximately 0.020 inches (0.5 mm) to approximately 0.080 inches (1.9 mm) or preferably from approximately 0.028 inches (0.7 mm) to approximately 0.063 inches (1.6 mm). However, a smaller screen size such as 0.028 inches (0.7 mm) is observed, and low treatment of a product is incurred. With a larger screen size such as 0.063 inches (1.6 mm), a result of an increase in distribution of granules larger than 850 μm is incurred. With the screen size in the vicinity of approximately 0.040 inches (1.0 mm), excessive distribution of granules with the size larger than 850 μm is excluded without remarkably lowering treatment.

[0145]

The changes in the aforementioned wet-type granulation and wet-type crushing parameter are used for adjusting the granular size distribution. For example, a slight reduction in the granular size is observed as mixing time is increased in a mixture containing a small quantity of water. If water concentration is too low, a binding agent to be used cannot be sufficiently activated, a cohesive power between the primary particles in the granule is not sufficient, and it is assumed that there is a shearing force generated by friction of the granular size rather than a mixing blade and growth. To the contrary, the cohesive power between the primary particles becomes larger by an increase in the quantity of water for sufficiently activating the binding agent, the shearing force is generated by the mixing blade and the granular growth rather than friction generated in the increased mixing time and/or water adding speed. The fluctuation in the screen size of the wet-type mill has a larger influence on the granular size than the fluctuation in the feed rate and/or mill speed.

[0146]

Then, the dried granules are arranged in an appropriate blender such as a twin-shell type blender, and a lubricating agent (magnesium stearate) and an additional carrier material (microcrystalline cellulose outside the granule and/or croscarmellose sodium outside the granule in specific tablet formulation) are selectively added so as to make a final blend mixture. The blending time partially depends on a process device in use. In the aforementioned 100-mg dosage capsule and the 200-mg dosage capsule (1080 kg and 918 kg batches), a blend material having extremely uniform celecoxib concentration was obtained in a blending time of at least approximately 5 minutes with a blender load within a range from approximately 15% to approximately 60% and a blender rotation speed of at least approximately 10 times per minute consistently. A relative standard deviation measured for a blend sample of a unit dosage was 3.9% or less and 2.2% or less for each of the 100-mg and 200-mg dosage capsules. The diluting agents include microcrystalline cellulose, and it was found that addition of the microcrystalline cellulose at a certain portion during the aforementioned process drastically improves granular compressibility and tablet hardness. In addition, by increasing the aforementioned magnesium stearate in the quantity from approximately 1% to approximately 2%, it was observed that the hardness of the tablet decreases and crushability and dissolution time increase.

[0147]

The aforementioned final blend mixture is then encapsulated (or if a tablet is to be prepared, it is compressed to a tablet with a desired weight and hardness by using a tool of an appropriate size). Conventionally publicly-known compression and encapsulation arts which are publicly known to a person ordinarily skilled in the art are used. An appropriate result of the capsule was obtained by using a height of a bed within a range from approximately 20 mm to approximately 60 mm, consolidation setting within a range from approximately 0 to approximately 5 mm, and a speed from approximately 60,000 capsules to 130,000 capsules per hour. Weight control of the dosage was observed and is decreased by either one of (i) low speed and high compression and (ii) high speed and a high bed height. Therefore, the combination of the aforementioned parameters is carefully controlled. It was also found that slug formation is minimized or excluded by using the lowest consolidation setting at which the capsule weight control is maintained. If a tablet with coating is needed, a person ordinarily skilled in the art can use a conventional publicly-known coating art.

[0148]

By means of combinations of unit works, a granule whose celecoxib content is

uniform at a unit dosage level and which is easily disintegrated and flows sufficiently easily is manufactured, the weight fluctuation is controlled to a reliable degree during capsule filling or making tablets, bulk density is sufficient, batch treatment is possible in a selected device, and individual dosages are compatible with a specific capsule or tablet die.

L. [0161]

Example 4: 200-mg dosage tablet

The tablet was prepared so as to have the following components.

[0162]

[Table 4] ...

The prepared tablet was a tablet having a deformed capsule shape of 0.275 inches × 0.496 inches (6.6 mm × 11.9 mm).

[0164]

[Table 5] ...

Example 6: Dissolution test

Dissolution speeds of capsules in Example 1 and Example 2 and tablets in Example 3 and Example 4 were acquired by using a device of the USP method 2 (with a spatula). Uncoated tablets were used for the purpose of the aforementioned test. A solution in 1000 ml with 1% of sodium lauryl sulfate / 0.04 M Na_3PO_4 (pH = 12) was used as a liquid for dissolution. The solution was maintained at a temperature of 37±5°C and was agitated at 50 rpm during the test. 12 pieces of the same tablets or capsules were tested. The 12 tablets or capsules were individually placed on one of 12 standard dissolution vessels, and a solution portion in 5 ml was taken out of each of the vessels after 15, 30, 45, and 60 minutes, respectively. A sample from each of the vessels was filtered, and absorbance of the samples was measured (UV spectrometer; quartz cell with 2 mm optical path; 243 nm or maximum wavelength of UV; blank is dissolution medium). On the basis of the measured absorbance, a dissolution rate was calculated. Average results of the dissolution test are listed in Table 6. The solubility at high pH in the aforementioned test conditions does not indicate solubility in a gastrointestinal tract.

[0165]

[Table 6] ...

Example 7: Particle size analysis

Table 7A illustrates a result of screen analysis of a particle size of the pharmaceutical composition subjected to the wet-type granulation in Example 1 and Example 2, respectively, prior to encapsulation. The phrase "rate held on the screen"

means a weight% of all the batches having the particle size larger than a pointed-out screen size.

[0166]

[Table 7] ...

Table 7B illustrates a result of screen analysis of a particle size of the pharmaceutical composition subjected to the wet-type granulation in Example 3 and Example 4, respectively, prior to compression to tablets. The phrase "rate of a batch" means a weight% of all the batches having the particle size between the pointed-out screen size and the next small screen size. The phrase "rate of accumulated batches" reports weight% of all the batches having the particle size larger than the pointed-out screen size.

[0167]

[Table 8] ...

M. [0170]

Example 11: Bioavailability by dog model

A healthy female beagle dog having a weight of 9 to 13 pounds (4.1 to 5.9 kg) was administered with one session of the following celecoxib: (1) subsequent to intravenous infusion of 5.0 mg of celecoxib per body weight kg, second intravenous infusion of 5.0 mg of celecoxib per body weight kg; (2) 5 mg of celecoxib in the oral solution form per body weight kg; (3) 5.0 mg of neat unblended celecoxib in the oral capsule form per body weight kg are administered. The vehicle for intravenous and oral solution administration was a mixture of polyethylene glycol having an average molecular weight 400 (PEG-400) and water in a volume ratio of 2:1. Each of the intravenous infusions was divided into two sessions of infusion and given in 15 to 30 minutes with a 15-minute interval.

[0171]

Many blood samples were collected from each animal by venipuncture or an indwelling catheter to a heparinization tube. The celecoxib concentration in the serum was measured by HPLC, and the result data was used for calculating the pharmacokinetic parameters indicated in the following Table 11-1.

[0172]

[Table 12] ...

Example 11-2: Relative bioavailability of formulation by dog model

The effects of blending parameters such as the celecoxib particle size, an increase concentration of the humidifying agent, pH, and a celecoxib dispersed solution as a suspension were evaluated for the bioavailability by the dog model to the oral solution.

The effect that celecoxib is pulverized (average particle size of 10 to 20 μm) before blending was tested with a composition A. A combined effect of the pulverization, added humidifying agent (sodium lauryl sulfate), and increased microenvironment pH (Na_3PO_4 $12H_2O$) was tested with a composition B. The effect of bringing the humidifying agent (Tween 80) into close contact with celecoxib (effect of coprecipitation to simple dry mixing) was tested with a composition C. Moreover, the effects of the pulverized particle size (approximately 1 μm) and dispersion of the particles in the suspension were tested with a composition D. A celecoxib solution similar to that used in Example 11-1 (composition E) was used as a reference. In addition, data of Example 11-1 of uncrushed and unblended celecoxib in the capsule (composition F) were also put as a reference. Specific compositions of formulation A, B, C, D, E, and F are listed in Table 11-2A.

[0173]

[Table 13] ...

(1) Precipitation was made from an ethanol solution by using an aqueous solution of 5% polysorbate 80 as an antisolvent.

(2) A slurry was prepared as a suspension by ball-milling a drug with a slurry of polysorbate 80 and polyvinylpyrrolidone until the particle has a diameter of approximately 1μm when evaluated by a microscope.

(3) A solution of PEG-400 and water in a volume ratio of 2:1

The aforementioned composition was administered to a group of three male dogs and three female dogs. A solution E containing celecoxib in 5 mg per body weight kg and capsule formulations A and B in selective transfer design was administered to the dogs of a group 1. A capsule formulation C and a suspension D containing celecoxib in 5 mg per body weight kg in selective transfer design was administered to the dogs of a group 2. Blood plasma samples were collected for 24 hours, and celecoxib was analyzed by HPLC.

[0174]

From the results of the aforementioned experiments (Tables 11-2B, 11-2C, and 11-2C), reduction of the particle size (composition A) or coprecipitation of celecoxib with the humidifying agent (composition C) increased bioavailability of celecoxib (measured as $AUC_{(0\text{-}24)}$) as compared with early studies on unblended celecoxib illustrated in Example 11-1. The bioavailability of celecoxib increased from PEG-400/aqueous solution (composition E) to the suspension (composition D). The bioavailability from the suspension having the particle size of approximately 1 μm is similar to the bioavailability from the solution, and it is strongly suggested that the

bioavailability of celecoxib from the wet-type granulated solid composition can be improved by a small celecoxib particle size (by pin milling of celecoxib prior to blending, for example), increased wettability of celecoxib (by allowing sodium lauryl sulfate to be contained in the granular liquid, for example), and improved dispersion (by allowing croscarmellose sodium to be contained by granulation, for example). The bioavailability indicated in Tables 11-2C and 11-2D for each blending shows the bioavailability of the aforementioned blending as a ratio of the experimentally measured bioavailability to the intravenous administration of celecoxib by using solution data (composition E) as a bridge between studies of Example 11-1 and Example 11-2.

[0175]

[Table 14] ...

[0176]

[Table 15] ...

[0177]

[Table 16] ...

N. [0183]

Example 13

A capsule having the following formulation was prepared and evaluated.

[0184]

[Table 20] ...

Celecoxib was crushed several times through a vibration mill having continuous small screen sizes (#14, #20, #40). The D_{90} particle size of the celecoxib particle added to the aforementioned mixture was approximately 37 μm or less. Celecoxib, lactose, and polyvinylpyrrolidone were mixed in a planetary mixer bowl and wet-type granulated by using water. After that, the granules were dried in a tray at 60°C, crushed through a 40-mesh screen, wetted by magnesium stearate by a V-blender, and encapsulated by a dosator-type encapsulation machine. In-vitro dissolution profiles of the capsules were determined by using USP 2 method and 15 mM of phosphate buffer solution as a dissolution medium. After 15 minutes, approximately 50% in-vitro dissolution was achieved, and after approximately 30 minutes, 95% or more of in-vitro dissolution was achieved.

[0185]

The absorption, distribution, metabolism, and elimination profiles of the 100-mg unit dosage capsules described above were compared with the suspension profile of ^{14}C-celecoxib. The study was an open label random crossover study performed on

healthy male subjects. Suspensions were prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80, and the mixture was added to apple juice prior to administration. Subjects having received suspensions took a 300 mg dose of celecoxib. Subjects having received celecoxib in the capsule form received 3 capsules of a dose of the 100-mg dosage unit of celecoxib in order to administer 300 mg of celecoxib in total. The rate of absorption from the capsule was slower than that of the suspension, but was comparable to the suspension when measured at AUC ($_{0\text{-}48}$). Average results are reported in Table 13B below. Celecoxib was mostly metabolized to either urine or feces only by approximately 2.56% of radiation dosage.
[0186]
[Table 21] ...
O. [0188]
Example 15: Preparation of 100-mg dosage capsule

100 mg or 200 mg of celecoxib was administered, and each of the capsules having the composition shown in Example 1 or Example 2 was prepared according to the method shown in Figure 1 or Figure 2 on the basis of a pharmaceutically acceptable manufacture. 100 mg or 200 mg of celecoxib was given, and each of the tablets with the composition shown in Example 3 or Example 4 was prepared by changing the suitable method shown in Figure 1 or Figure 2, and instead of encapsulating the composition, it was made into a tablet, and addition of croscarmellose sodium and microcrystalline cellulose was used.
[0189]

In a method which describes bulk mixing of capsules of 100 mg administration utilizing the following starting substances, a typical batch consists of 4 identical granulation sections, but the number of granulation sections is not strictly critical and depends mainly on the throughput of the device and a required batch size.
[0190]
Crushing

Celecoxib was mixed on an impact pin mill with counter-rotating discs. At a milling speed within a range from approximately 8960 rpm/5600 rpm (rotation rpm / counter-rotation rpm) to 112000 rpm/5600 rpm, the particle size was varied within a relatively narrow range (D_{90} is 30 μm or less), suggesting that the milling speed is not strictly critical to a bulk drug pulverization process. Figure 2 illustrates a process system diagram showing a preferred working example wherein a celecoxib starting substance is pulverized in an impact mill or preferably a pin mill, prior to blending with a carrier material.

[0191]

Dry mixing

Celecoxib, lactose, polyvinylpyrrolidone, and croscarmellose sodium were transferred to a 1200 L Niro fielder PMA-1200 high-speed granulator and mixed by a high-speed chopper and an impeller for approximately 3 minutes. In this dry mixing time, sufficient mixing of the carrier material and celecoxib could be achieved prior to initiation of the wet-type granulation step.

[0192]

Wet-type granulation

Sodium lauryl sulfate (8.1 kg) was dissolved in purified USP water (23.7 kg). The resulting solution was continuously added to the granulator at a rate of approximately 14 kg/min. The total granulation time was approximately 6.5 minutes. During this granulation, a main blade and a chopper blade of the granulator were disposed at a high speed setting. The wet-type granulated mixture contained water of approximately 8.1 weight%. Alternatively, in the dry mixing step, sodium lauryl sulfate may be mixed with celecoxib, lactose, polyvinylpyrrolidone, and croscarmellose sodium, and purified USP water may be added to the dry mixture containing sodium lauryl sulfate.

(2) According to the described matter of the aforementioned (1), it is found that the present description has the following disclosure in relation with Present Invention 1.

A. Celecoxib which is an inhibitor of cyclooxygenase-2 is abnormally hardly dissolved in an aqueous medium and if unblended celecoxib is orally administered in a capsule form; for example, since it is rapidly absorbed in a gastrointestinal tract, it is not easily dissolved or disintegrated. Moreover, the unblended celecoxib having a crystalline form with a tendency of forming a long and coagulated needle is usually fused at compression on a tablet molding die and becomes a monolithic bulk. When it is blended with another substance, the celecoxib crystal has a tendency of being separated from another substance, coagulates with celecoxib during mixing of the composition, and becomes a non-uniform blending composition containing an unnecessarily large mass of celecoxib. Therefore, it is difficult to prepare a pharmaceutical component containing celecoxib having desired blend uniformity, which is a problem, and thus, there has been a need of blending orally deliverable celecoxib with improved bioavailability and the like in the unblended celecoxib, and it was particularly useful to provide blending indicating pharmacokinetics with rapid efficacy rather than capability of unblended celecoxib ([0003], [0006], [0008], [0009]).

B. The "present invention" is a pharmaceutical composition containing one or more orally deliverable dosage units, and each unit contains particle celecoxib in a quantity from approximately 10 mg to approximately 1000 mg closely mixed with one or more pharmaceutically acceptable excipients and has a configuration having distribution of celecoxib primary particle size so that D_{90} is approximately 200 μm or less in the longest size of the particle (90% of the sample particles are smaller than the D_{90} value) ([0011], [0013]).

2. Common general technical knowledge or well-known arts at the time of priority date of the present application

(1) Exhibits Ko A7, 16, 23, 65 to 68, 80, Exhibit Ko B1, Exhibit Ko C7, and Exhibits Otsu 2 and Otsu 3 have the following descriptions.

A. Exhibit Ko A7 ("Elution of pharmaceuticals" (published on October 30, 1977)

(a) "When a surface area is increased by reducing a particle diameter, a dissolution speed should be able to be increased. However, only the increase of the surface area is not enough, and it is an effective surface area that should be increased. The effective surface area is a surface area where a drug is in contact with a test liquid. If the drug is hydrophobic and wetting by a solvent is poor, cohesion occurs when the particle diameter is reduced, and as the result of rather reduction of the effective surface area, the dissolution speed can be slowed in some cases." (page 104, lines 14 to 10 from bottom).

(b) "By adding 0.2% of polysorbate 80 to the eluted solution, phenacetin is rapidly dissolved, and in this case, the dissolution speed increases as the particle diameter is reduced. It is considered that, by adding polysorbate 80, the solvent wets the surface of the drug powder well, and the dissolution speed increases as the degree of crushing (page 106, lines 3 to 6).

(c) "The fact that the smaller the particle diameter of the drug in use, the more elution speeds from granules of phenacetin and phenobarbital increase is illustrated in Figure 4.4 and Figure 4.5. The reason is that, since the surface of the drug powder body becomes hydrophilic during granulation, the smaller the particle diameter, the more the effective surface area increases." (page 108, lines 8 to 11)

(d) "The smaller the powder body, the larger the specific surface area. Moreover, since the hydrophobic surface becomes hydrophilic by the granulation, the effect of the granulation appears in the finest powder body the most strongly." (page 109, lines 2 to 3).

(e) "From the studies made in this field, the following conclusion can be made in

general. That is, by reducing the particle diameter of the drug in a tablet, elution and absorption are expedited. The cause for that probably lies in an operation involved in the tablet manufacture. That is, when the drug is mixed with a hydrophilic excipient for granulation, the surface of the drug which is originally hydrophobic becomes hydrophilic." (page 111, lines 4 to 7)

B. Exhibit Ko A16 ("Design and evaluation of orally administered pharmaceuticals" (published on February 10, 1995)

(a) "Means for pulverizing pharmaceutical particles is used most as a method for increasing the surface area." (page 168, line 10).

(b) "When a particle diameter is reduced by pulverization, the dissolution speed is increased by an increase in the surface area." (page 168, line 18)

(c) "It is reported in many poorly soluble drugs... that bioavailability can be improved by pulverization." (page 168, lines 23 to 25)

(d) "However, as particles become finer, cohesion occurs more easily, and the surface area (effective surface area) in contact with water is, to the contrary, decreased by crushing, and the dissolution speed decreases in some cases. Particularly hydrophobic substances have strong cohesiveness. ... When a surfactant is present here, the fine particles are not coagulated but uniformly dispersed in the solution, and the smaller the particle size, the higher the elution speed. ... In such a case, means of crushing by adding a fluidizer or a surfactant as a pulverization aid is taken for the purpose of preventing cohesion." (page 168, line 4 from bottom to page 169, line 4)

C. Exhibit Ko A17 (Micronization: A method of Improving the Bioavailability of Poorly Soluble Drugs" (published in April of 1998), abridged translation thereof is as follows)

"In poorly soluble drugs, digestion absorption depends on the dissolution speed thereof. By reducing the particle size of these drugs, the dissolution speed is improved. A pulverization mill, that is, either one of a ball mill and a fluid-energy mill, is used for pulverizing the powder. These processes were applied to griseofulvin, progesterone, spironolactone, and diosmin. For each of the drugs, their digestion absorption and their bioavailability and consequently clinical effectiveness were improved by pulverization."

D. Exhibit Ko A23 ("Solid pharmacology and bioavailability" (published on February 4, 1981))

"(2) Particle diameter of drug

In a drug with a relatively small solubility in water, the dissolution speed is greatly different depending on the particle diameter of a drug powder in the

pharmaceutical. In general, the dissolution speed of a substance from a particle follows the rule of Noyes - Whitney indicated in formula 4-1.

-dM/dt = KS (Cs - C) ... formula 4-1

Where M denotes a quantity of the substance in a particle state and thus, dM/dt is a dissolution speed, K is a constant determined by a temperature, solvent, and an agitating condition, S is a surface area of the particle, Cs is solubility of the substance, and C is concentration of the substance at time t. As is obvious from this formula, the dissolution speed increases in proportion to the surface area S of the particle. And with regard to a certain quantity of particles, the larger the surface area per unit volume, that is, the larger the specific surface area, the higher the dissolution speed." (page 38, line 5 from bottom to page 39, line 5)

E. Exhibit Ko A65 ("Development of pharmaceuticals" (published on May 20, 1990))

"In the case of poorly soluble drugs, since the solubility is low, a concentration gradient of a dispersion layer on the particle surface is small, and the elution speed becomes lower. The concentration gradient of the dispersion layer is changed also by the agitation speed, but it is not largely changed in vivo. The dissolution speed can be made faster by making the particles smaller so as to increase the specific surface area." (page 53, lines 6 to 3 from bottom)

F. Exhibit Ko A66 ("New pharmaceutics" (published on September 10, 1993)

"Crushing is to destroy particles by applying a mechanical external force and to reduce the particle diameter and is one of important unit operations in a pharmacological process.

Main objects of the crushing are [i] to allow smoother chemical reactions by increasing the specific surface area of the particle; [ii] to facilitate mixing with other component particles and the like. If sizes of the component particles are remarkably different, they should be crushed in advance prior to mixing so that they have the same degree of particle diameters in order to obtain a uniform mixture." (page 212, lines 6 to 15)

G. Exhibit Ko A67 ("Pharmaceutics" (revised version) (November 1, 1982 (date of publishing first print of revised version)

"When a dried material powder is prepared in a pharmaceutical process, the first operation to be performed is crushing. ... Main reasons among those cited as the purposes of crushing are:

1) To increase the specific surface area of a powder body exposed to chemical reactions; and
2) To facilitate mixing with other component powder bodies and the like. ... It is

widely known that the particle diameter has an influence on bioavailability of a solid pharmaceutical, but they are all related to the specific surface area." (page 170, lines 9 to 16)

H. Exhibit Ko A68 ("Pharmaceutics" (revised third version) (April 1, 1997 (revised third version published)

"The crushing is a unit operation for reducing the particle diameter of a solid particle to an appropriate size. The purpose of the crushing is not only improvement of physical properties such as an increase in the dissolution speed but also expectation of improvement in uniformity of mixing between material powder bodies including additives of the solid pharmaceutical, increase in granulation performances, and moreover, increase in mechanical strength of granules and tablets from a viewpoint of pharmaceutical technology." (page 168, lines 14 to 11 from bottom)

I. Exhibit Ko A80 ("Design and evaluation of orally administered pharmaceuticals" (published on February 10, 1995))

"If the material is in a needle crystal, since it is bulky and poor not only in filling performance but also in fluidity, for example, it is often crushed for granulation." (page 92, lines 1 to 2)

J. Exhibit Ko B1 ("Prescription design of orally administered pharmaceuticals" (published on April 15, 1998)

"(a) Crushing

The crushing is an operation for reducing the particle diameter by applying a mechanical external force such as impact, compression, friction, and the like to a solid sample, and its purpose is to reduce the particle diameter, to increase the dissolution speed, to improve oral absorbability of poorly water-soluble drug, to uniformize a mixed state, to improve moldability at tableting, and the like.

In general, the crushed/pulverized powder bodies have high surface energy, are susceptible to an influence of electrostatics, and have high adhesion/cohesiveness and thus, handling becomes complicated. Moreover, since stability might be lowered with the change in the crystalline state, if a crushing operation is incorporated in the manufacturing process, the influence on the product substance needs to be examined." (page 51, lines 12 to 4 from bottom)

K. Exhibit Ko C7 ("Bulletin of Japanese Association of Crystal Growth" (published on July 1, 1981)

"In the case of poorly soluble drugs, to make them microcrystalline is desirable in order to improve bioavailability, but this increases adhesion/cohesiveness and leads to degradation of secondary physical properties such as fluidity or filling performances."

(page 427, left column, lines 16 to 12 from bottom)

L. Exhibit Otsu 2 ("Prescription design of orally administered pharmaceuticals" (published on April 15, 1998)

"(a) Increase in particle diameter by granulation

The fluidity of the powder body tends to become poorer as the particle diameter is reduced. ... Therefore, if the particle diameter can be increased by any means, the fluidity can be improved. That is, the increase in the particle diameter by a granulation operation falls under this, and this is also the reason why the granulation powdered drugs are generally used recently." (page 157, lines 12 to 13, page 159, lines 2 to 4)

M. Exhibit Otsu 3 ("Pharmaceutics" (revised third version) (April 1, 1997 (revised third version published)

(a) "In general, the larger the angle of repose, the poorer the fluidity of the powder body. The relationship between the angle of repose and the particle diameter is ... the angle of repose becomes smaller as the particle diameter increases." (page 69, lines 2 to 3)

(b) "c Improvement of fluidity

The following methods are tried in order to improve the fluidity of the powder body.

[ii] The particle diameter is made larger by granulation" (page 70, lines 1 to 5)

(2) By summarizing the described matters in the aforementioned (1), it is found to be well known or common general technical knowledge at the time of the present priority date that [i] elution of drugs is improved by reducing the particle diameter of the drug by crushing so as to increase the specific surface area (effective surface area), while for poorly soluble drugs, if wettability by the solvent is poor, cohesion can occur easily when the particle diameter is reduced, and as the result of reduced effective surface area, the dissolution speed can be slowed in some cases and fluidity of the powder body is worsened by microminiaturizing the particle, and cohesion occurs easily in some cases; [ii] even for the hydrophobic poorly soluble substance, if a surfactant is present, the fine particles do not coagulate but are uniformly dispersed in the solution, and the smaller the particle size, the higher the elution speed.

3. Reason for rescission 4 (error in judgment of support requirement)

Plaintiffs allege that it cannot be recognized from the description in the Detailed Description in the present description and the common general technical knowledge at the time of the present priority date that a person ordinarily skilled in the art could

have solved the problem of Present Invention 1 over the entire range of the numeral values that "celecoxib particle D_{90} is less than 200 μm in the maximum length of the particle" in Present Invention 1 and thus, Present Invention 1 does not conform to the support requirement and Present Inventions 2 to 5 and 7 to 9 do not conform to the support requirement, either, and the judgment of the JPO decision that Present Inventions 1 to 5 and 7 to 19 conform to the support requirement is erroneous, which will be judged in the following.

(1) Conformity of Present Invention 1 to support requirement

A. Article 36, paragraph 6, item (i) of the Patent Act prescribes that the description of the Scope of Claims should not exceed the scope of the invention described in the Detailed Description of the Invention, and the gist is understood that, if the invention not described in the Detailed Description of the invention is described in the Scope of Claims, it is equal to a claim for a monopolistic and exclusive right to the invention having not been published, which is not appropriate, and this should be prevented.

Then, it is reasonable to understand whether or not the description in the Scope of Claims conforms to the requirement provided for in the item (support requirement) for the invention including a predetermined numeral value range in the invention specifying matter should be determined by examining whether it can be recognized that a person ordinarily skilled in the art could solve the problem of the invention over the entire range of the numeral values included in the invention from the description in the Detailed Description of the Invention and the common general technical knowledge at the time of filing.

By examining this for Present Invention 1, according to the description in the Scope of Claims (Claim 1) of Present Invention 1, Present Invention 1 is an invention related to a "pharmaceutical composition containing an orally deliverable solid dosage unit" containing "fine particle celecoxib in a quantity from 10 mg to 1000 mg closely mixed with one or more pharmaceutically acceptable excipient" and is characterized by "having particle size distribution of celecoxib particles D_{90} less than 200 μm in a maximum length of a particle" and thus, it can be considered to be an invention including a predetermined numeral value range in the invention specifying matter.

Then, according to the disclosed matter of the present description in the aforementioned 1(2), Present Invention 1 is found to have a problem to provide a pharmaceutical composition containing solid orally deliverable celecoxib particles whose bioavailability is improved with respect to unblended celecoxib.

B(a) The Detailed Description of the Invention in the present description has descriptions related to the bioavailability of celecoxib that "the composition of the

invention has particle distribution of celecoxib so that particle D_{90} is approximately 200 μm or less, preferably approximately 100 μm or less, more preferably 75 μm or less, further preferably approximately 40 μm or less, or most preferably approximately 25 μm or less in a maximum length of the particle. Usually, the bioavailability of celecoxib is improved by a reduction in the particle size of celecoxib according to the aforementioned working example of the present invention." ([0022]), "It was found that bioavailability of celecoxib is improved by reduction in the celecoxib particle size when it is orally administered in the form of a capsule or a tablet. Therefore, the celecoxib D_{90} particle size is approximately 200 μm or less, preferably approximately 100 μm or less, more preferably approximately 75 μm or less, further preferably approximately 40 μm or less or the most preferably 25 μm or less. As exemplified in Example 11, for example, by reducing the celecoxib D_{90} particle size as a start material from approximately 60 μm to approximately 30 μm, the bioavailability of the composition is drastically improved. In addition or alternatively, celecoxib has an average particle size within a range from approximately 1 μm to approximately 10 μm or preferably from approximately 5 μm to approximately 7 μm." ([0124]), "In the wet-type granulation process, celecoxib is first crushed or pulverized to a desired particle size (together with one or more carrier material, if necessary). Various mills or crushers can be used, but by using impact crashing such as pin milling of celecoxib, improved blending uniformity can be realized in the final composition as compared with other types of crushing. For example, to cool celecoxib by using liquid nitrogen is needed during crushing in order to avoid heating of celecoxib to an unnecessary temperature. As described above, it is important to reduce the D_{90} particle size to approximately 200 μm or less, preferably to approximately 100 μm or less, more preferably to approximately 75 μm or less, further preferably to approximately 40 μm or less, or most preferably to approximately 25 μm or less during the aforementioned crushing process for the bioavailability of celecoxib to increase." ([0135]). These descriptions can be considered to indicate that if the unblended celecoxib is crushed to have the "celecoxib D_{90} particle size less than approximately 200 μm", the bioavailability of celecoxib is improved, and the improved blending uniformity can be realized in the final composition by impact crushing by the pin milling of celecoxib or the like as compared with other types of crushing.

On the other hand, [i] the Scope of Claims (Claim 1) of Present Invention 1 does not have description prescribing a specific method configured by "having distribution of celecoxib particles D_{90} less than 200 μm in a maximum length of a particle" or does

not have description that the "fine particle celecoxib" in Present Invention 1 is limited to those crushed by "impact crushing such as pin milling", either, or rather, paragraph [0135] in the present description has the description that "Various mills or crushers can be used" in relation to the pulverization of celecoxib; [ii] paragraph [0008] in the present description has the description that "Celecoxib is abnormally hardly dissolved in a water-soluble medium. If it is orally administered in a capsule form, for example, since unblended celecoxib is rapidly absorbed in a gastrointestinal tract, it is not easily dissolved or dispersed. In addition, the unblended celecoxib having a crystalline form with a tendency of forming a long and coagulated needle is usually fused at compression on a tablet molding die and becomes a monolithic bulk. When it is blended with another substance, the celecoxib crystal has a tendency of being separated from the another substance, coagulates with celecoxib during mixing of the composition, and becomes a non-uniform blending composition containing an unnecessarily large mass of celecoxib."; and [iii] In view of the fact that, at the time of priority date of this case, it was well known or common general technical knowledge that elution of the drug is improved by reducing the particle diameter of the drug by crushing so as to increase the specific surface area (effective surface are), while for a poorly soluble drug, if wettability by the solvent is poor, cohesion can occur easily when the particle diameter is reduced, and as the result of reduced effective surface area, the dissolution speed can be slowed in some cases and fluidity of the powder body is worsened by microminiaturizing the particle, and cohesion occurs easily in some cases, it cannot be immediately understood that the bioavailability of celecoxib is improved by having the configuration that "celecoxib D_{90} particle size less than approximately 200 μm" for the celecoxib which is a poorly soluble drug.

Moreover, according to the description of the present description as a whole, there is no description on the technical meaning of specifying the distribution of the particle size by using the value of "D_{90}" of the celecoxib particle in the maximum length of the particle and specific explanation on the relations between the value of the "D_{90}" and the bioavailability.

However, the term "D_{90}" refers to the value of a particle diameter when the accumulated number of particles has reached 90%, while the phrase "D_{90} is less than 200 μm" in Present Invention 1 means that the ratio of the particles at 200 μm or more is limited so as not to exceed 10%, but since the particle diameter distribution of bulk drug of the poorly soluble drugs takes various forms depending on the compound (Exhibit Ko A72), it cannot be understood that the bioavailability is improved

whatever the particle diameter distribution of 90% of the particles is, so long as the ratio of the particles at 200 μm or more is limited.

According to the above, from the description in paragraphs [0022], [0124], and [0135] of the present description, it cannot be recognized that, if the "celecoxib D_{90} particle size is approximately 200 μm or less", the bioavailability of celecoxib is improved over the entire numeral value range.

(b) In this regard, Defendant alleges that [i] a mechanism for solving the problem of Present Invention 1 is that the bioavailability of celecoxib is improved by setting D_{90} in the maximum length of the celecoxib particle to be less than 200 μm so that cohesiveness of celecoxib having a property of easy cohesion is reduced, and as a result, the effective surface area of the celecoxib particles increases and the dissolution speed rises; [ii] when a pin mill is used, celecoxib becomes a microminiaturized uniform particles from a long needle state, while in the case where an air jet mill is used, the long needle state crystals remain, and a cohesive power is not improved easily when crushed by a liquid energy mill as compared with crushing by using the pin mill (paragraph [0024] in the present description) and thus, it was found not to be such that the celecoxib particles only need to be pulverized so as to reduce the average particle diameter, but the ratio of the long needle state crystals remaining in the pulverized particles is important, and the ratio needs to be limited, and in Present Invention 1, D_{90} in the maximum length of the particles remaining in the pulverized particles was used as a reference; [iii] the mechanism that the bioavailability is improved when celecoxib particle D_{90} in the maximum length is less than 200 μm or less can be confirmed in the description of the present description (paragraphs [0167], [0172] to [0177], [0183] to [0186], [0205], Table 11-2C, Table 11-2D); and [iv] it can be understood from the particle distribution diagram in Attachment 2-1 and Attachment 2-2 that the particle D_{90} prepared so that the average particle size is 1 μm or 10 to 20 μm becomes less than 200 μm.

However, the aforementioned description in the present description pointed out by Defendant does not have the technical meaning of specifying the distribution of the particle size by using the value of the celecoxib particle "D_{90}" in the maximum length of the particle or explanation on the relationship between the value of "D_{90}" and the bioavailability.

Moreover, as described in the aforementioned (a), the "fine particle celecoxib" of Present Invention 1 is not limited to those crushed by using the "pin mill" ("pin milling") and thus, the mechanism that the bioavailability is improved when D_{90} of the celecoxib particle in the maximum length is less than 200 μm cannot be grasped on

the premise that the "pin mill" is used.

Furthermore, Defendant states that, in Attachment 2-1 and Attachment 2-2, in the case of the average particle size of 1 μm or 10 to 20 μm in which the average particle diameter of D_{90} with 200 μm is approximately a center value (blue line) in the mountain-shaped distribution diagram in Attachment 2-1, and the average particle size (blue line) is approximately 100 μm which is a median thereof, the mountain-shaped distribution slides to a (left) direction where the particle diameter is smaller as a whole as in Attachment 2-2 and thus, D_{90} has a value smaller than 200 μm. But the particle diameter distribution of the bulk drug of a poorly soluble drug takes various forms depending on the compound (Exhibit Ko A72) as in the aforementioned (a). In view of the fact that the particle diameter distribution as in Figure [viii] in Exhibit Ko A72 ("D_{90} value ●●●● μm". Attachment 3) can be taken, for example, the particle diameter distribution in the case where D_{90} is less than 200 μm does not necessarily take the particle diameter distribution as alleged by Defendant.

Therefore, the aforementioned allegation by Defendant has no grounds.

(c) Moreover, Defendant alleges that the mechanism that the bioavailability is improved when D_{90} of the celecoxib particle in the maximum length is less than 200 μm can be understood from the description in the present description, and this understanding without an error can be confirmed also from the additional test results (Exhibit Otsu 10) indicating that the bioavailability of celecoxib D_{90} at 200 μm is improved as compared with the uncrushed celecoxib.

By examining that, there is a description in Exhibit Otsu 10 that the celecoxib capsule containing uncrushed celecoxib (D_{90} = 669 μm) (hereinafter referred to as the "uncrushed capsule") and the celecoxib capsule (containing celecoxib 25%, sodium lauryl sulfate 2%, and "Avicel PH-101" 73%, hereinafter referred to as the "196-μm capsule") containing microminiaturized celecoxib (D_{90} = 196 μm) by being crushed by the pin mill are administered to a "beagle dog", and the bioavailability was measured and as a result, the bioavailability was 16.1% for the uncrushed capsule, while it is 32.1% for the 196-μm capsule, and the 196-μm capsule was improved by a factor of 2.0.

On the other hand, in view of the fact that the present description has the description that "Celecoxib is not dissolved in an aqueous solution easily. Therefore, the pharmaceutical composition of the present invention arbitrarily but preferably includes one or more pharmaceutically acceptable humidifying agents as a carrier material. The humidifying agent is preferably selected so that celecoxib maintains affinity with water, and that state is considered to improve the relative bioavailability

of the pharmaceutical composition." ([0075]) and "Sodium lauryl sulfate is a preferable humidifying agent. If present, sodium lauryl sulfate is contained in a quantity from approximately 0.25% to approximately 7%, preferably from approximately 0.4% to approximately 6% or more preferably from approximately 0.5% to approximately 5% to the total weight of the composition." ([0076]) and in view of the fact that, even in the case of the hydrophobic poorly soluble substance, the fine particles do not coagulate but are uniformly dispersed in the solution if a surfactant is present, and the smaller the particle size, the faster the elution speed is well known or a common general technical knowledge at the time of the present priority date (aforementioned 2(2)), it is found that sodium lauryl sulfate contained in the 196-μm capsule as a humidifying agent is likely to influence the test result of the bioavailability of the 196-μm capsule.

Moreover, when the 196-μm capsule is blended, it is crushed by a pin mill to be microminiaturized, but as described in the aforementioned (a), the "fine particle celecoxib" in Present Invention 1 is not limited to those crushed by using the "pin mill".

Therefore, since the mechanism that the bioavailability is improved when the D_{90} of the celecoxib particle in the maximum length is less than 200 μm cannot be recognized from the test result of the Exhibit Otsu 1, the aforementioned allegation by Defendant cannot be employed.

C(a) The present description has the description on the experiment result of the "bioavailability by a dog model" as "Example 11" and the experiment result of the "bioavailability of formulation by a dog model" as "Example 11-2" ([0170] to [0177], Tables 11-1, 11-2A, 11-2B, 11-2C, 11-2D).

Example 11 and Example 11-2 have descriptions that the respective bioavailabilities were measured by administration by vinous injection of celecoxib, administration of oral solution form of celecoxib, and administration of uncrushed and unblended oral capsule of celecoxib by using a female dog and a male dog as models, as the result of measurement of the bioavailability for "composition A" to "composition F", for the female dog, the "composition A" (capsule containing pulverized celecoxib, sodium lauryl sulfate, and "Avicel 101") was 31.2%, the "composition B" (capsule containing pulverized celecoxib, sodium lauryl sulfate, "Avicel 101", tri-sodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$)) was 24.9%, and the "composition F" (uncrushed and unblended celecoxib) was 16.9% (Table 11-2C), while for the male dog, the "composition A" was 49.4%, the "composition B" was 54.2%, and the "composition F" was 16.9% (Table 11-2D). These descriptions

indicate that the bioavailability of the "composition A" and the "composition B" which contain pulverized celecoxib is higher than the bioavailability of the "composition F" which is uncrushed and unblended celecoxib.

Then, paragraph [0172] in the present description has the description that celecoxib is "pulverized (average particle size of 10 to 20 μm) before blending for the "composition A" but does not have explicit description on the celecoxib D_{90} particle size, but by considering the description in paragraph [0124] that "As exemplified in Example 11, for example, by reducing the celecoxib D_{90} particle size as a start material from approximately 60 μm to approximately 30 μm, the bioavailability of the composition is drastically improved.", the celecoxib D_{90} particle size contained in the "composition A" is presumed to be approximately 30 μm. Moreover, the same is also applied to the "composition B".

On the other hand, from the fact that the "composition A" and the "composition B" contain sodium lauryl sulfate in the weight ratio based on a dry weight of 2% and 25%, respectively (Table 11-2A), similarly to the description in the aforementioned B(c), in view of the descriptions in paragraphs [0075] and [0076] in the present description and the common general technological knowledge at the time of the present priority date (aforementioned 2(2)), sodium lauryl sulfate contained in the "composition A" and the "composition B" as the humidifying agent is found to be highly likely to influence the experiment results of the bioavailability.

Then, from the experiment results of the bioavailability of the "composition A" and the "composition B" in which the celecoxib particle D_{90} is approximately 30 μm, it cannot be recognized that the bioavailability is improved over the unblended celecoxib over the entire numeral value range of "the celecoxib particle D_{90} is less than 200 μm" in Present Invention 1.

(b) In response to that, Defendant alleges that the present description explicitly describes that sodium lauryl sulfate is contained in the "composition A" in Table 11-2A, but it is the effect of pulverization of celecoxib that is evaluated in the "composition A", and it is the effect of the increased humidifying agent by sodium lauryl sulfate that is evaluated in the "composition B" ([0172]), and from the fact that the bioavailability of the "composition B" containing 25% of sodium lauryl sulfate is lower than that of the "composition A" containing only 2% of sodium lauryl sulfate (Table 11-2C for female dogs) or substantially equal (Table 11-2D for the male dogs), it can be understood that the improvement effect of the bioavailability is not from sodium lauryl sulfate but from the pulverization of celecoxib.

However, in view of the fact that the present description has the description that

sodium lauryl sulfate considered to be a preferable humidifying agent is contained in a quantity from approximately 0.25% to approximately 7%, preferably from approximately 0.4% to approximately 6%, or more preferably from approximately 0.5% to approximately 5% with respect to the total weight of the composition ([0076]), the "composition A" contains 2% of sodium lauryl sulfate which is considered to be a preferable quantity, while the "composition B" contains 25% of sodium lauryl sulfate which remarkably exceeds the quantity considered to be preferable and thus, even if the "composition B" has the result of the bioavailability equal to or slightly lower than the "composition A", it cannot be recognized that the improvement result of the bioavailability is realized not by sodium lauryl sulfate but by pulverization of celecoxib.

Therefore, the aforementioned allegation by Defendant has no grounds.

D(a) The present description has the description ([0184] to [0186], Table 13B) of the experiment results of the relative bioavailability ($AUC_{(0-48)}$) using a capsule of D_{90} particle size at 37 μm or less of the celecoxib particle crushed several times with a suspension through a vibration mill including continuous small screen sizes (#14, #20, and #40) as "Example 13."

Example 13 has the description ([0185], [0186]) that, as the result of an experiment using a suspension profile of a 100-mg unit dosage capsule containing celecoxib with the D_{90} particle size at 37 μm or less and ^{14}C-celecoxib with a "healthy male" as a subject, the "bioavailability measured by "$AUC_{(0-48)}$" was equal to that of the suspension containing celecoxib for the 100-mg unit quantity capsule containing the celecoxib particle with the D_{90} particle size at 37 μm or less.

However, in view of the fact that Example 13 does not have description on the particle size of the celecoxib contained in the suspension, and the particle size is not known, it cannot be recognized that the bioavailability is improved over the unblended celecoxib over the entire numeral value range of "D_{90} of the celecoxib particle is less than 200 μm" in Present Invention 1 from the aforementioned experiment result in which D_{90} of the celecoxib particle is approximately 37 μm or less.

(b) On the other hand, Defendant alleges that, in Example 13 in the present description, it was confirmed that when the suspension considered to be prepared by the method similar to Example 11-2 (the particle size is approximately 1 μm diameter) and a capsule with the D_{90} particle size at approximately 37 μm or less were administered to the same subject, their $AUC_{(0-48)}$ were equal, and even when the D_{90} particle size at 37 μm, it exerts an effect similar to that at 1 μm and thus, a person

ordinarily skilled in the art can expect with high probability that even the celecoxib with the D_{90} particle size at 37 μm or more exerts improved bioavailability as compared with the bioavailability of the uncrushed celecoxib containing the particle size larger than the size of 420 μm.

However, the suspension in Example 11 was "(2) Prepared as a suspension by ball-milling a drug with a slurry of polysorbate 80 and polyvinylpyrrolidone until the particle has a diameter of approximately 1μm when evaluated by a microscope." ([0173]), while the suspension in Example 13 was "prepared by dissolving celecoxib in ethanol containing 5% Polysorbate 80" ([0185]), and since the preparation methods of the suspension are different, Defendant's allegation that the particle size of the suspension in Example 13 is "approximately 1 μm diameter" lacks premise.

Moreover, in view of the fact that the present description has the description that the celecoxib particle of the capsule prepared in Example 13 was obtained such that "Celecoxib, lactose, and polyvinylpyrrolidone were mixed in a planetary mixer bowl and wet-type granulated by using water" ([0184]) and the description that "Polyvinylpyrrolidone is a preferable binding agent used for applying cohesiveness to celecoxib powder blend and other excipients for granulation of celecoxib blending.", "The cohesive power is applied to the powder blend by polyvinylpyrrolidone, required binding occurs easily, and granules are formed during wet-type granulation.", and "the composition of the present invention including polyvinylpyrrolidone is prepared particularly by wet-type granulation and it was found to indicate relatively improved bioavailability over the other compositions." ([0074]), it can be recognized that it is probable that the bioavailability of the celecoxib particle in the capsule prepared in Example 13 was improved by wet-type granulation using polyvinylpyrrolidone.

Therefore, the aforementioned allegation by Defendant has no grounds.

E. Subsequently, "Example 15" in the present description has the description that "the particle size was varied within a relatively narrow range (D_{90} is 30 μm or less)" as a crushing method for "preparing a capsule of 100-mg dosage" ([0190]), but this experiment result is not related to the bioavailability of celecoxib.

Other than the above, the present description has no disclosure of an experiment result related to the particle size of the celecoxib particle D_{90} and the bioavailability.

F. According to the above, since it cannot be found that a person ordinarily skilled in the art could have solved the problem of Present Invention 1 over the entire numeral value range of "the celecoxib particle D_{90} is less than 200 μm in the maximum length of the particle" included in Present Invention 1 from the description in the Detailed Description of the Invention in the present description and the common general

technical knowledge at the time of the present priority date, Present Invention 1 cannot be found to conform to the support requirement.

The judgment in this JPO decision different from that is an error.

(2) Conformity to support requirement of Present Inventions 2 to 4

Present Invention 2 has the invention specifying matter that "the celecoxib particle D_{90} is less than 100 μm in the maximum length of the particle", Present Invention 3 has the invention specifying matter that "the celecoxib particle D_{90} is less than 40 μm in the maximum length of the particle", and Present Invention 4 has the invention specifying matter that "the celecoxib particle D_{90} is less than 25 μm in the maximum length of the particle".

Then, it cannot be found that Present Invention 1 that "the celecoxib particle D_{90} is less than 200 μm in the maximum length of the particle" conforms to the support requirement as in the aforementioned (1).

Subsequently, as found in the aforementioned (1)C, the present description has the description of the experiment result of the bioavailability of the "composition A" and the "composition B" in which the celecoxib particle D_{90} is approximately 30 μm as Example 11 and Example 11-2, but in view of the fact that it is found that sodium lauryl sulfate contained as the humidifying agent in the "composition A" and the "composition B" is highly likely to influence the experiment result of the bioavailability, it cannot be recognized from the aforementioned experiment result that in the case where D_{90} has a value smaller than approximately 30 μm, the bioavailability improved over the unblended celecoxib. Moreover, as found in the aforementioned (1)D, the present description has the description of the experiment result of the relative bioavailability using the capsule of the celecoxib particle D_{90} particle size at 37 μm or less as Example 13, but in view of the fact that it is probable that the bioavailability of the capsule was improved by wet-type granulation using polyvinylpyrrolidone, it cannot be recognized that the bioavailability is improved over the unblended celecoxib from the aforementioned experiment result in the case where D_{90} has a value smaller than approximately 37 μm.

Then, although Present Inventions 2 to 4 have an upper limit value of the value of the "celecoxib particle D_{90} in the maximum length of the particle" lower than that of Present Invention 1, it cannot be recognized that a person ordinarily skilled in the art could have solved the problem of Present Invention 1 over the entire numeral value range of the value of the "celecoxib particle D_{90} in the maximum length of the particle" included in Present Inventions 2 to 4 from the description in the Detailed Description of the Invention in the present description and the common general

technical knowledge at the time of the present priority date similarly to Present Invention 1.

Therefore, Present Inventions 2 to 4 cannot be found to conform to the support requirement.

(3) Conformity of Present Inventions 5, 7 to 19 to support requirement

Present Inventions 5, 7 to 19 (Claims 5, 7 to 19) include the pharmaceutical composition described in Claim 1 in the invention specifying mater, but since Present Invention 1 cannot be recognized to conform to the support requirement as described in the aforementioned (1), Present Invention 5 and Present Inventions 7 to 19 cannot be found to conform to the support requirement, either.

(4) Summary

As described above, since Present Inventions 1 to 5 and 7 to 19 cannot be found to conform to the support requirement, the judgment of the present JPO decision different from that is erroneous.

4. Conclusion

According to the above, since the reason for rescission 4 alleged by Plaintiffs has grounds, the present JPO decision should be rescinded even without a need to judge the other reasons for rescission.

Intellectual Property High Court, Fourth Division
Presiding Judge; OTAKA Ichiro
Judge: FURUKAWA Kenichi
Judge: OKAYAMA Tadahiro

(Attachment 1)

[Table 4]

Table 4

Component	Quantity/tablet (mg)	Weight ratio (%)	Quantity/batch (kg)
Celecoxib	200	40	6.40
Lactose monohydrate (NF)	203.75	40.75	6.52
Sodium lauryl sulfate (NF)	15	3	0.48
Povidone (K29/32, USP)	12.5	2.5	0.40
Croscarmellose (Avicel PH-102, NF)	15	3	0.48
Microcrystalline cellulose (Type A, NF)	50	10	1.60
Magnesium stearate (NF)	3.75	0.75	0.12
Total quantity	500	100	16
Opadry white YS-1-18027A	15.0		

[Table 5]

Table 5

Tablet	Disintegration time
Example 3: 100-mg dosage tablet (without coating)	4 minutes 35 seconds
Example 4: 200-mg dosage tablet (without coating)	7 minutes 40 seconds

[Table 6]

Table 6

Composition	Dissolution ratio %			
	15 minutes	30 minutes	45 minutes	60 minutes
Example 1: 100-mg capsule	89	99	100	100
Example 2: 200-mg capsule	55	82	89	92
Example 3: 100-mg tablet	81	93	94	95
Example 4: 200-mg tablet	60	96	98	98

[Table 7]

Table 7A

Screen size (μm)	Rate held by screen			
	Example 1: 100-mg capsule		Example 2: 200-mg capsule	
	lower limit	upper limit	lower limit	upper limit
850	0	1.3	1.1	10.7
425	2.8	14.9	4.3	25.4
250	10.0	25.5	10.8	35.4
180	15.3	39.0	17.3	39.2
106	32.5	64.5	35.2	58.2
75	37.1	77.5	39.5	71.8
0	100	100	100	100

[Table 8]

Table 7B

Screen size (μm)	Example 3: 100-mg tablet		Example 4: 200-mg tablet	
	rate of batch	rate of accumulated batches	rate of batch	rate of accumulated batches
840 (20 mesh screen)	1	1	0.79	0.79
420 (40 mesh screen)	24.6	25.6	24.85	25.64
250 (60 mesh screen)	18.4	44	19.13	44.77
177 (80 mesh screen)	9.6	53.6	11.05	55.82
149 (100 mesh screen)	6.6	60.2	6.9	62.72
105 (140 mesh screen)	11.6	71.8	11.44	74.16
74 (200 mesh screen)	8.8	80.6	8.28	82.45
fine	19.4	100	17.55	100

[Table 12]

Table 11-1

Pharmacokinetics parameter	Intravenous injection	Oral solution	Capsule unblended
C_{max} (ng/ml)	6950	2190	517
T_{max} (h)	Not applied	0.5	3.0
$AUC_{0-\infty}$ (ng/ml) h	31200	16200	4800
Clearance (ml/min.kg)	3.08	5.14	17.4
$T_{1/2}$ (h)	8.84	9.15	11.8
Bioavailability (%)	Not applied	57.1	16.9

[Table 13]

Table 11-2A

Component	Weight ratio based on dry weight (%)					
	A	B	C	D	E	F
Celecoxib (pulverized)	25	25				
Celecoxib/tween 80(1)			25			
Celecoxib (dispersed) (2)				100		
Celecoxib (solution) (3)					100	
Celecoxib (uncrushed)						100
Sodium lauryl sulfate	2	25				
Avicel 101	73	25	75			
$Na_3PO_4H_2O$		25				
Total	100	100	100	100	100	100

[Table 14]

Table 11-2B

time (hours)	Serum celecoxib concentration (μg/ml)					
	A	B	C	D	E	F
0	0	0	0	0	0	0
0.5	0.0143	0.247	0.0635	0.453	0.824	0.205
1.0	0.244	0.228	0.443	0.826	0.820	0.333
2.0	0.318	0.138	0.717	0.865	0.604	0.262
3.0	0.189	0.0860	0.492	0.741	0.517	0.517
4.0	0.145	0.0707	0.384	0.576	0.413	0.234
6.0	0.107	0.0664	0.233	0.354	0.286	-
7.0	-	-	-	-	-	0.197
8.0	0.0828	0.0624	0.160	0.234	0.187	-
12.0	0.0939	0.0431	0.0865	0.142	0.0802	-
24.0	-	0.0404	0.0408	0.0394	0.0159	-

[Table 15]

Table 11-2C

Pharmacokinetics parameter	Value for female dogs					
	A	B	C	D	E	F
C_{max} (ng/ml)	360 ±60	250 ± 70	790 ± 190	1010 ± 270	840 ± 240	500
T_{max} (h)	1.3 ± 0.2	0.7 ± 0.2	1.5 ± 0.3	1.7 ± 0.44	0.67 ± 0.18	3.0
Bioavailability (%)	31.2 ± 2.9	24.9 ± 1.4	46.3 ± 9.5	69.5 ± 9.6	62.4 ± 9.4	16.9

[Table 16]

Table 11-2D

Pharmacokinetics parameter	Value for male dogs					
	A	B	C	D	E	F
C_{max} (ng/ml)	520 ± 110	450 ± 180	640 ± 260	830 ± 330	1520 ± 200	500
T_{max} (h)	5.3 ± 3.3	3.3 ± 1.3	1.5 ± 0.5	5.7 ± 3.42	1.5	3.0
Bioavailability (%)	49.4 ± 12.0	54.2 ± 13.1	42.9 ± 13.1	87.5 ± 20.6	89.4 ± 4.5	16.9

[Table 20]

Table 13A

Component	Quantity (mg)		
	5-mg capsule	20-mg capsule	100-mg capsule
Celecoxib	5	20	100
Lactose	92	77	61.9
Povidone (K29-32)	2.5	2.5	4
Magnesium stearate	0.5	0.5	0.8
Total	100	100	166.7
Cell of capsule	1	1	1
Size of capsule	#3	#3	#3

[Table 21]

Table 13B

Pharmacokinetics parameter	Suspension	Capsule
$AUC_{(0-48)}$((ng/ml)h)	8706.7	8763.1
C_{max} (ng/ml)	1526.5	1076.5
T_{max} (h)	1.42	1.94
$T_{1/2}$ (h)	11.53	15.57

(Attachment 2-1)

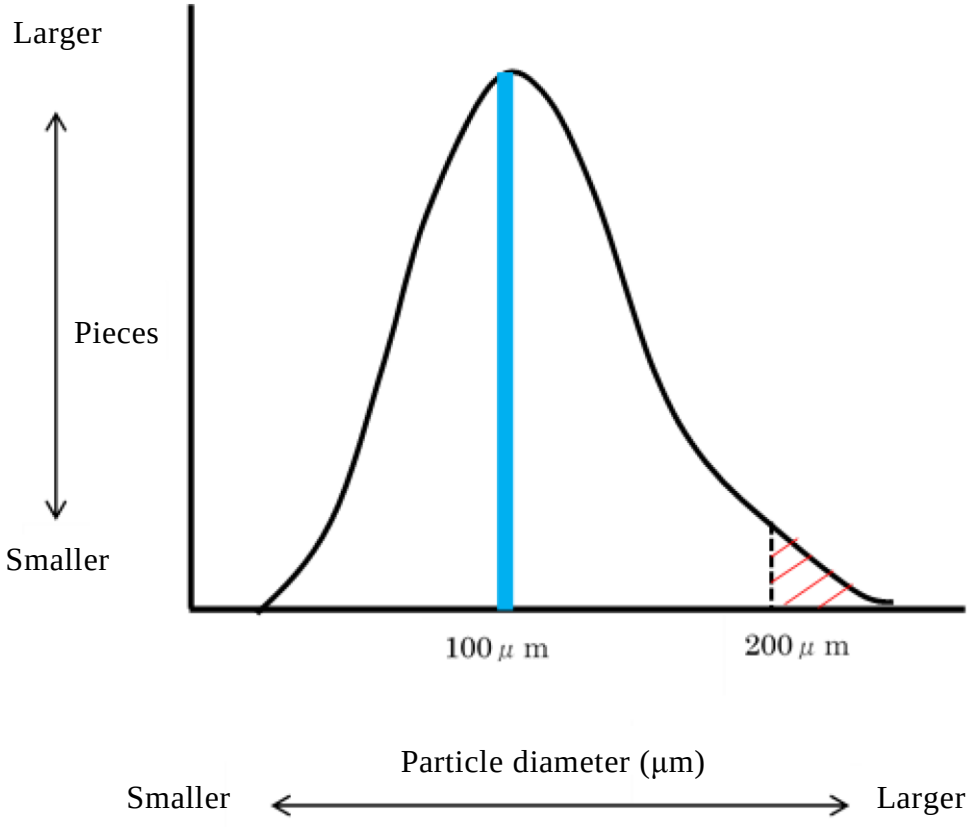


Figure 1: Particle distribution diagram when D_{90} is 200 μm

(Attachment 2-2)

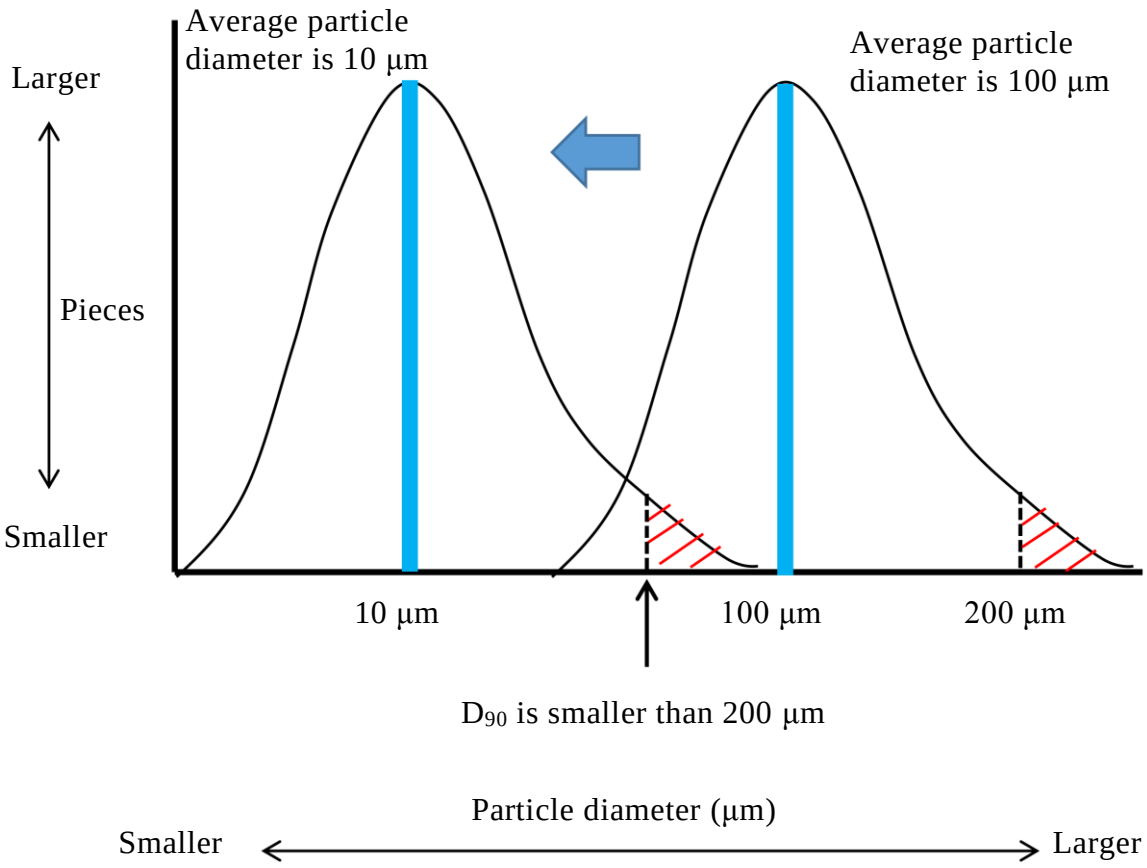


Figure 2: When the average particle diameter becomes smaller, the particle distribution diagram shifts to a direction of smaller particles

(Attachment 3)