(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 November 2009 (19.11.2009)

PCT

(10) International Publication Number
WO 2009/139589 A2

(51) International Patent Classification:
A61K 9/08 (2006.01)

(21) International Application Number:
PCT/KR2009/002567

(22) International Filing Date:
14 May 2009 (14.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2008-0044481 14 May 2008 (14.05.2008) KR

(71) Applicant *(for all designated States except US)*: **SK HOLDINGS CO., LTD.** [KR/KR]; 99 Seorin-dong, Jongro-gu, Seoul 110-110 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAEK, Myoung-Ki** [KR/KR]; 102-305 Mujigae Apt., Wolpyeong 2-dong, Seo-gu, Daejeon 302-750 (KR). **JO, Jae-Hoon** [KR/KR]; 105-1407 Gukhwa Apt., Samcheon-dong, Seo-gu, Daejeon 302-222 (KR). **CHANG, Hye-Jin** [KR/KR]; 103-805 Mokryeon Apt., Dunsan-dong, Seo-gu, Daejeon 302-120 (KR).

(74) Agent: **C&S LOGOS PATENT AND LAW OFFICE**; 13th Floor, Seocho-Pyunghwa Building, 1451-34 Seocho-dong, Seocho-gu, Seoul 137-070 (KR).

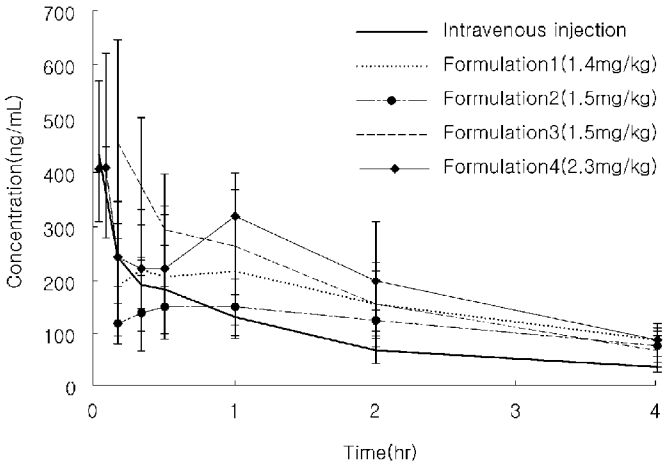
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: TRANSNASAL ANTICONVULSIVE PHARMACEUTICAL COMPOSITION COMPRISING POORLY SOLUBLE ANTICONVULSANT

[Fig. 1]



(57) Abstract: There is provided a transnasal anticonvulsive pharmaceutical composition including a poorly soluble anticonvulsant. The anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray- administered, comprises diethylene glycol monoethyl ether and fatty acid ester, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20. Also, the anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray-administered, comprises diethylene glycol monoethyl ether, fatty acid ester, methylpyrrolidone, water and alcohol. Therefore, the transnasal anticonvulsive pharmaceutical composition may be useful to highly enhance the bioavailability of the poorly soluble anticonvulsant. Also, the transnasal anticonvulsive pharmaceutical composition may be useful to allow the poorly soluble anticonvulsant to show the improved viscosity and/or enhanced solubility in order to effectively deliver the poorly soluble anticonvulsant at a therapeutic dose.

WO 2009/139589 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Description

TRANSNASAL ANTICONVULSIVE PHARMACEUTICAL COMPOSITION COMPRISING POORLY SOLUBLE ANTICONVULSANT

Technical Field

[1] The present invention relates to a transnasal anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant, and more particularly, to a transnasal anticonvulsive pharmaceutical composition having enhanced bioavailability to be effectively delivered at a therapeutic dose, and improved viscosity and/or enhanced solubility to show desirable properties such as spray angle and spraying shape.

[2]

Background Art

[3] Status epilepticus is a neurologically emergent condition, leading to 3-35% mortality. The chief target for treatment of status epilepticus is to swiftly manage pathological attacks. However, when the symptoms of status epilepticus last for a long time without the swift management, it is difficult to control the status epilepticus, and the risk of permanent brain damage increases. Therefore, it is very important to swiftly treat patients by administering to the patients an adequate dose of a pharmaceutical composition having an adequate pharmaceutical formulation containing an effective drug. Recently, it has been known that a variety of pharmacotherapies are used to treat the status epilepticus. Diazepam and lorazepam are benzodiazepine drugs that have been most widely used for this purpose. Also, the intravenous administration of an anticonvulsant is the swiftest way to suppress epileptic convulsions. However, when the intravenous administration is not easy, for example, when the intravenous administration is delayed due to the technical difficulty such as the lack of a sterilizer and a skilled practitioner, and when there is phlebitis to possibly develop, it may be more desirable to administer an anticonvulsant via other routes. Also, intravenous drugs are often associated with hypotension, cardiac dysrhythmia or central nervous system degeneracy. In this regard, Moolenar, et al. made an attempt to administer diazepam to human beings via various routes such as intramuscular injection, oral tablet and rectal solution (Int. J. Pharm., 5: 127- 137(1986)), but they found that the rectal administration of the diazepam provides its highly swift absorption. Therefore, it may be considered that the rectal administration is used as an alternative to an intravenous injection. Kenneth L., et al. has developed the rectal formulation (US Patent 5462740) as a useful method. This rectal route of administration is a very uncomfortable route

used for the emergency treatment and the drug administration to patients with age over the adolescent period.

[4] Nasal mucosae provide a virtual route for therapeutic effects of many medicinal substances. The nasal administration has an advantage in that drugs may be easily and simply administered to achieve systemic or topical effects, when necessary. In particular, zolmitriptan (US Patent 5,466,699), which had been developed as one of drugs for the central nervous system to treat migraine, was developed and commercially available as a nasal spray formulation (US Patent 6,750,237), and sumatriptan (US Patent 5,037,845) was also developed and commercially available as a nasal spraying agent. However, unlike the two water-soluble drugs, most of drugs hardly have solubility corresponding to a desired therapeutic dose, and one leading problem associated with the nasal administration of drugs may not be solved by the simple transnasal administration means since most of drug molecules are not easily or are slowly spread through the nasal mucosae. An additional restriction on the nasal administration of drugs is that the drugs are restrictedly administered in a small dose. In general, it is impossible to administer drugs in a dose of approximately 150 ul or more per nostril, and an amount of a mixture exceeding the dose range of the drugs are extruded into the pharynx, and swallowed.

[5] Also, the drugs such as diazepam and lorazepam are difficult to be developed into a formulation suitable for nasal spray administration since they have low solubility in water that is widely used to dissolve drugs. Therefore, the development of solvents for nasal spray administration, which dissolve a desired drug, for example, diazepam and lorazepam, in a high concentration and give no stimulus to the nasal mucosae, is highly required.

[6] The nasal absorption of drugs may be augmented by administering the drugs and a chemical aid or a penetration enhancer at the same time. For example, Lau and Slattery [Lau, et al., Int. J. Pharm., 54: 171-174(1989)] made an attempt to dissolve benzodiazepine (i.e. diazepam) in various solvents (for example, triacetin, dimethyl sulfoxide, PEG 400, Cremophor EL, Lipal-9-LA, diisopropyl adipate and azone) and administer the dissolved drug.

[7] However, the diazepam was dissolved in most of the solvents within a desired concentration, but the desired concentration of the solvents is too pungent to be used for transnasal administration. Cremophor EL has been known to have the lowest stimulus to the nasal mucosal tissue, but its nasal absorption is rather slow (T_{max}: 1.4 hours) in humans in use of these vehicles, and the peak concentration is lower than that observed after the intravenous administration. Recently, Li, et al. (International Journal of Pharmaceutics Vol. 237, pp77-85, 2002) proposed a microemulsion for rapid-onset transnasal delivery of diazepam.

[8] Also, US 6,627,211 B1 (KR 2002-0059583) discloses transnasal anticonvulsive compositions comprising diazepam. Here, the diazepam is dissolved in a soluble formulation such as aliphatic alcohol, a polar solvent (i.e. glycol), water, etc. Also, US 2005-0002987 A1 (KR 2006-0012030) discloses a transnasal administration composition used for transnasal microemulsions containing diazepam. Here, the diazepam is dissolved in a vehicle comprising equivalent amounts of fatty acid ester and water and the balance of hydrophilic surfactant, polar solvent (i.e. glycol), etc.

[9] When drugs are nasally administered to patients, their fine and uniform dispersion is important. A spraying shape test used to evaluate the efficiency of a nasal spraying agent has been widely used to evaluate a nasal administration formulation *in vitro*. This spraying shape test is important since the *in vivo* delivery of a drug is possible when the drug uniformly distributed following its nasal spraying. For example, USA test standards on the spraying shape test has been set, and must be reproducible and be suitable for these test standards in order to deliver a suitable drug to treat its corresponding disease (U. S. Food and Drug Administration's (FDA) Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Spray for Local Action (June 1999)).

[10] According to the report by Yang, et al. (Pharmaceutical Research Vol22, No.11, pp.1871-1878, 2005), a formulation having a small droplet size and low viscosity is delivered to central and inner regions of the nasal cavities, which indicates that the formulation is more desirably distributed nasally than formations having a big droplet size and high viscosity. Therefore, it is important that the nasal formulation has a viscosity and droplet size suitable for the purpose of drug delivery.

[11]

Disclosure of Invention

Technical Problem

[12] An aspect of the present invention provides a pharmaceutical composition having physical properties suitable for the transnasal administration, such as enhanced bioavailability of a poorly soluble anticonvulsant, viscosity and/or solubility, etc.

[13] Another aspect of the present invention provides a method for treating convulsions including: administering to patients suffering from the convulsions a sufficient amount of a pharmaceutical composition to treat the convulsions.

[14]

Technical Solution

[15] According to an aspect of the present invention, there is provided an anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray-administered, the anticonvulsive pharma-

ceutical composition including diethylene glycol monoethyl ether and fatty acid ester, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20.

[16] According to another aspect of the present invention, there is provided an anti-convulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray-administered, the anticonvulsive pharmaceutical composition including diethylene glycol monoethyl ether, fatty acid ester, methylpyrrolidone, water and alcohol.

[17] According to still another aspect of the present invention, there is provided a method for treating convulsions, the method including: transnasally spray-administering to patients suffering from the convulsions a sufficient amount of the pharmaceutical composition to treat the convulsions.

[18]

Advantageous Effects

[19] As described above, the transnasal anticonvulsive pharmaceutical composition according to one exemplary embodiment of the present invention may be useful to highly enhance the bioavailability of the poorly soluble anticonvulsant.

[20] Also, the transnasal anticonvulsive pharmaceutical composition according to one exemplary embodiment of the present invention may be useful to allow the poorly soluble anticonvulsant to show the improved viscosity and/or enhanced solubility in order to effectively deliver the poorly soluble anticonvulsant at a therapeutic dose.

[21]

Brief Description of Drawings

[22] FIG. 1 shows a pharmacokinetic profile after intravenous (i.v) and transnasal administration of formulations containing diazepam as an anticonvulsant according to one exemplary embodiment of the present invention.

[23] FIG. 2 shows a pharmacokinetic profile after intravenous (i.v) and transnasal administration of formulations containing lorazepam as an anticonvulsant according to one exemplary embodiment of the present invention.

[24] FIG. 3 shows a spray pattern obtained by spraying a formulation according to one exemplary embodiment of the present invention using a nasal spray.

[25]

Best Mode for Carrying out the Invention

[26] Hereinafter, exemplary embodiments of the present invention will be described in detail.

[27] The present inventors have found that, when an anticonvulsive pharmaceutical com-

position containing a poorly soluble anticonvulsant as an active component, which is used for transnasal administration, include diethylene glycol monoethyl ether and certain fatty acid ester in the use of a minimum content of water and ethanol or without use of the water and ethanol, the solubility of diazepam in the anticonvulsive pharmaceutical composition is enhanced by up to 15.39%, compared to 2.5% as in US Patent 6,627,211 and 4.1% as in US Patent Application No. 2005-0002987, and the bioavailability of the diazepam is enhanced by up to 119%, compared to 65% as in both the above patents. Also, they have found that lorazepam widely used in clinical use is also nasally delivered to show 35% bioavailability. Therefore, the present invention was completed on the basis of the above facts.

[28] The present invention provides an anticonvulsive pharmaceutical composition, which is nasally sprayed for the purpose of transnasal administration, contains as an active component a poorly soluble anticonvulsant selected from the group consisting of diazepam and lorazepam, and further include diethylene glycol monoethyl ether and fatty acid ester, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20.

[29] According to the present invention, the diazepam or lorazepam used as the active component is preferably present in a content of 1 to 20 % by weight, based on the total weight of the pharmaceutical composition, but the present invention is not particularly limited thereto.

[30] The diethylene glycol monoethyl ether used in the present invention is preferably present in a content of 45 to 60 % by weight, based on the total weight of the pharmaceutical composition. For example, Transcutol P (commercially available from Gattefosse) may be used as the diethylene glycol monoethyl ether.

[31] The fatty acid ester used in the present invention includes caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20, and they may be used alone or in combinations thereof. In this case, the fatty acid ester is preferably present in a content of at least 30 % by weight or more, based on the total weight of the pharmaceutical composition. More preferably, the fatty acid ester is present in a content of 30 to 50 % by weight, based on the total weight of the pharmaceutical composition.

[32] According to one exemplary embodiment of the present invention, the pharmaceutical composition of the present invention includes 5 to 15 % by weight of at least one poorly soluble anticonvulsant selected from the group consisting of diazepam and lorazepam, 45 to 60 % by weight of diethylene glycol monoethyl ether, and 35 to 50 % by weight of fatty acid ester, wherein the fatty acid ester includes at least one selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate,

oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20. More preferably, at least one selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, and polysorbate 20 may be used as the fatty acid ester.

[33] Also, according to another exemplary embodiment of the present invention, there is provided an anticonvulsive pharmaceutical composition, which is transnasally spray-administered, containing as an active component at least one poorly soluble anti-convulsant selected from the group consisting of diazepam and lorazepam, the anti-convulsive pharmaceutical composition including diethylene glycol monoethyl ether, fatty acid ester, methylpyrrolidone, water and alcohol.

[34] According to this exemplary embodiment of the present invention, the diazepam or lorazepam is preferably present in a content of 1 to 20 % by weight, based on the total weight of the pharmaceutical composition, but the present invention is not particularly limited thereto. Also, the diethylene glycol monoethyl ether is preferably present in a content of 45 to 60 % by weight, based on the total weight of the pharmaceutical composition. For example, Transcutol P (commercially available from Gattefosse) may be used as the diethylene glycol monoethyl ether.

[35] The fatty acid ester used according to this exemplary embodiment of the present invention includes, but is not particularly limited to, caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, polysorbate 20 and propylene glycol monocaprylate, and they may be used alone or in combinations thereof. Therefore, the fatty acid ester is preferably present in a content of at least 30 % by weight or more, based on the total weight of the pharmaceutical composition. More preferably, the fatty acid ester is present in a content of 30 to 50 % by weight, based on the total weight of the pharmaceutical composition.

[36] More preferably, methyl laurate is used as the fatty acid ester, and is present in a content of at least 30 % by weight or more, based on the total weight of the pharmaceutical composition. More preferably, the fatty acid ester is present in a content of 30 to 50 % by weight, based on the total weight of the pharmaceutical composition.

[37] In addition, propylene glycol monocaprylate is preferably used as the fatty acid ester. In this case, the propylene glycol monocaprylate is preferably present in a content of 5 to 25 % by weight, based on the total weight of the pharmaceutical composition, but the present invention is not particularly limited thereto.

[38] Additionally, the alcohol used according to this exemplary embodiment of the present invention preferably includes, but is not particularly limited to, ethanol.

[39] Also, according to one exemplary embodiment of the present invention, the pharmaceutical composition of the present invention contains 5 to 15 % by weight of at least

one poorly soluble anticonvulsant selected from the group consisting of diazepam and lorazepam, and also 40 to 60 % by weight of diethylene glycol monoethyl ether, 5 to 15 % by weight of methyl laurate, 5 to 30 % by weight of methylpyrrolidone, 1 to 5 % by weight of water and 5 to 10 % by weight of ethanol.

[40] Also, the pharmaceutical composition according to one exemplary embodiment of the present invention may further include dimethyl isosorbide. In this case, the dimethyl isosorbide is preferably present in a content of 5 to 10 % by weight, based on the total weight of the pharmaceutical composition, but the present invention is not particularly limited thereof.

[41] The pharmaceutical composition according to one exemplary embodiment of the present invention preferably has a fluid kinematic viscosity of 10 ㎟/sec or less so that it can be transnasally spray-administered. Therefore, the pharmaceutical composition according to one exemplary embodiment of the present invention is easy to be nasally administered. The nasal administration is characterized in that this method is highly simple, compared to other methods of parenteral administrations, and such low viscosity allow a drug to be effectively delivered in a desired therapeutic dose by using a commercially available nasal spray. A pharmaceutical composition having a poorly insoluble drug dissolved therein may not be delivered using a conventional nasal spray since the pharmaceutical composition has a high viscosity, and therefore it is necessary to use a nasal spray for high-viscosity compositions or an available high-pressure pump. In this regard, the pharmaceutical composition according to one exemplary embodiment of the present invention may be constantly absorbed and stably administered using a conventional nasal spray system such as uni-dose, bi-dose and multi-dose spray devices (commercially available from Pfeiffer), and Acuspray spray (BD).

[42] According to another exemplary embodiment of the present invention, there is provided a method for treating convulsions including: transnasally spray-administering to patients suffering from the convulsions a sufficient amount of the pharmaceutical composition to treat the convulsions.

[43] The pharmaceutical composition according to one exemplary embodiment of the present invention has an advantage in that the solubility of diazepam in the anticonvulsive pharmaceutical composition is enhanced by up to 15.39%, compared to 2.5% as in US Patent 6,627,211 and 4.1% as in US Patent Application No. 2005-0002987, and the bioavailability of the diazepam is enhanced by up to 119%, compared to 65% as in both the above patents, as corroborated in Examples described later. Also, the pharmaceutical composition has an advantage in that lorazepam widely used in clinical tests also shows 35% bioavailability, which indicates that the bioavailability of the poorly soluble anticonvulsant is highly enhanced. Therefore, the transnasal anticonvulsive pharmaceutical composition according to one exemplary em-

bodiment of the present invention is made very easy to be administered. When compared to the parenteral administration, for example, a simple spray, a dropper, or a nebulizer may be especially used to satisfy the requirements regarding the rapid and convenient delivery of drugs for emergency treatment of an acute convulsive attack of epilepsy. In the clinical term, the transnasal administration often makes it possible to enhance the duration of anticonvulsive activity. A therapeutic dose of the transnasal anticonvulsive pharmaceutical composition may be more effectively and exactly controlled by administering the formulation of the present invention once or several times. Although the anticonvulsant is described as a model compound in the present invention, the present invention is applicable to other biological activators that may be used for mucosal administration to humans and animals.

[44]

Mode for the Invention

[45] Hereinafter, exemplary embodiments of the present invention are now described in more detail. However, it should be understood that the description proposed herein is just a preferable example for the purpose of illustrations only, not intended to limit the scope of the invention.

[46]

[47] Example 1: Preparation of Solution for Transnasal Administration

[48] Diethylene glycol monoethyl ether and fatty acid ester were put into a paddle-type stirrer, and completely mixed. Then, a hydrophobic solvent, water and ethanol were sequentially added, and mixed with the resulting mixture, when necessary. Here, the expression "omplete mixing" means a state where the mixture solution is clear and transparent without any of phase separation and turbidity.

[49]

[50] Example 2: Solubility Test of Diazepam

[51] 100 mg of diazepam was added to 500 $\mu\ell$ of the mixture prepared in the method of Example 1 so that each formulation can have its composition ratio as listed in the following Tables. Then, the resulting mixture was stirred at a room temperature for 24 hours, and then filtered through a 0.45-micrometer membrane filter. Then, the resulting filtrate was subject to liquid high performance liquid chromatography to analyze a concentration of diazepam. A column used in this experiment was a 10 mm C18 column with 30 cm x 3.9 mm, and a mobile phase was a mixture (by volume ratio) composed of 65% of methanol and 35% distilled water. A flow rate was set to 1.4 mL/min, and the detection was performed at a wavelength of 254 nm. *p*-Hydroxyanisole was used as an analytical internal standard substance. The results are listed in the following Tables 1 to 8. In the final solution in which diazepam is dissolved, each component is rep-

resented by a final composition ratio (% by weight.

[52] Table 1

[Table 1]

[Table]

(Formulation 1)

Components	Final composition ratio (% by weight)
Diethylene glycol monoethyl ether	48.3%
Caprylocaproyl polyoxylglyceride	24.3%
Oleoyl polyoxylglyceride	7.3%
Sorbitan monolaurate 20	10.9%
Diazepam	9.13%

[53]

[54] Table 2

[Table 2]

[Table]

(Formulation 2)

Components	Final composition ratio (% by weight)
Diethylene glycol monoethyl ether	48.64%
Caprylocaproyl polyoxylglyceride	24.36%
Isopropyl palmitate	7.30%
Sorbitan monolaurate 20	10.95%
Diazepam	8.75%

[55]

[56] Table 3

[Table 3]

[Table]

(Formulation 3)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	48.54%
Caprylocaproyl polyoxylglyceride	24.32%
Isopropyl palmitate	7.29%
Polysorbate 20	10.93%
Diazepam	8.92%

[57]

[58] Table 4

[Table 4]

[Table]

(Formulation 4)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	45.38%
Caprylocaproyl polyoxylglyceride	15.13%
Sorbitan monolaurate 20	16.76%
Isopropyl palmitate	11.17%
Distilled water	4.65%
Diazepam	6.91%

[59]

[60] Table 5

[Table 5]

[Table]

(Formulation 5)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	56.64%
Sorbitan monolaurate 20	8.50%
Oleoyl polyoxylglyceride	5.66%
Methylpyrrolidone	17.70%
Diazepam	11.5%

[61]

[62] Table 6

[Table 6]

[Table]

(Formulation 6)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	42.61%
Propylene glycol monocaprylate	21.30%
Methyl laurate	10.75%
Dimethyl isosorbide	7.10%
Methylpyrrolidone	7.10%
Diazepam	11.23%

[63]

[64] Table 7

[Table 7]

[Table]

(Formulation 7)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	41.56%
Methyl laurate	8.66%
Propylene glycol monocaprylate	6.93%
Methylpyrrolidone	20.78%
Distilled water	1.73%
Ethanol	6.93%
Diazepam	13.41%

[65]

[66] Table 8

[Table 8]

[Table]

(Formulation 8)

Components	Final composition ratio(% by weight)
Diethylene glycol monoethyl ether	40.61%
Methyl laurate	8.46%
Methylpyrrolidone	27.08%
Distilled water	1.69%
Ethanol	6.77%
Diazepam	15.39%

[67]

[68] Example 3: Viscosity Measurement

[69] A capillary viscometer (Cannon-Fenske-Routine viscometer) was used as the viscometer, and the viscosity was measured at a constant temperature of 40℃ in a water bath by using the viscometer attached to a fixing apparatus. A suction tube was used to transfer the mixture prepared in Example 2 according to the method of Example 1 to a starting line of the viscometer. Then, the mixture was kept for approximately 10 min so that it can drop along a capillary tube, and the time required for

the dropping of the mixture was measured. The kinematic viscosity was calculated as represented by the following Equation 1. Here, a viscosity unit was represented by mm ^{2}/sec.

[70] Equation 1

[71] Kinematic viscosity ( ) = Viscometer constant (K= 0.01547 mm^2/s^2) elution time (t)

[72] Table 9

[Table 9]

[Table]

Viscosity measurement results

Formulations	mm2/sec
Formulation 1	17.1
Formulation 2	14.5
Formulation 3	17.7
Formulation 4	15.5
Formulation 5	8.5
Formulation 6	2.93
Formulation 7	2.23
Formulation 8	1.97

[73]

[74] Example 4: Evaluation of Spray Pattern

[75] A trace of an edible blue pigment was mixed with the mixture of the prepared formulation 2, and the resulting mixture was loaded into a nasal spray (a bi-dose system, Pfeiffer), and then sprayed twice on a white filer positioned 3 centimeters from the nasal spray, thus to analyze a spray pattern. The results are shown in FIG. 3 (Left - Primary spraying, Right - Secondary spraying).

[76] The spray pattern was oval, which is close to round, and the ovality ratios were 1.25 in the primary spraying (Left photograph of FIG. 3) and 1.0 in the secondary spraying (Right photograph of FIG. 3), as represented by a ratio of maximum diameter (D_{max}) to minimum diameter (D_{min}) of the oval spray pattern. US Food and Drug Administration (FDA) regulations for inhaled and nasal drug products (Guidance for industry, Nasal spray and inhalation solution, suspension and spray drug products, chemistry, manufacturing, and controls documentation, 2002) recommends an ovality ratio of 1.0 to 1.3. Therefore, it was confirmed that the transnasal anticonvulsive pharmaceutical composition according to one exemplary embodiment of the present invention shows desirable spray angle and spraying shape so that it can be effectively delivered at a

therapeutic dose.

[77]

[78] Example 5: Pharmacokinetic test of diazepam-containing nasal formulation in rabbit (Bioavailability test)

[79] Right before this experiment, rabbits (n=3) were weighed, and a mixed solution including 25 mg of ketamine and 4 mg of xylazine was intramuscularly injected to the rabbits per kilogram (Kg) in order to anesthetize the rabbits, and a catheter was fastened to each rabbit to collect blood from rabbits otic artery. An intravenous injection was performed by administering the mixed solution to the rabbits via the rabbits otic artery at a dose of 1 mg/kg for approximately 20 seconds. A Melode injection (diazepam, 10 mg/2 mL; Dong Wha Pharm. Ind. Co. Ltd.) was used as intravenous injection. In order to transnasally administer each of the formulations 1, 2, 3 and 7 prepared in Example 2 to one nostril of each rabbit, a concentration of diazepam in the formulations 1, 2 and 3 was set to 8%, and its dosage was set to1.4 mg/kg. Also, a concentration of diazepam in the formulation 4 was set to 10%, and its dosage was set to 2.3 mg/kg. Then, each formulation was sprayed to the rabbits using a Pfeiffer nasal spry system. For the formulations prepared in Example 2, 8% diazepam is dissolved in the case of the formulations 2 and 3, and 10% diazepam is dissolved in the case of the formulation 4.

[80] Blood samples (1 ㎖) were collected from the rabbits otic artery at 0, 2, 5, 10, 20, 30, 45, 60 and 120 minutes after the intravenous injection and transnasal administration of each formulation. Each of the blood samples was centrifuged to separate rabbit plasma, which was stored at -20℃ until it is will be used for analysis. In order to analyze the plasma samples, each of the plasma samples (0.5 ㎖) was exactly transferred to a 1.5 ㎖ polypropylene centrifuge tube. The mixture was vortexed for 30 seconds, and centrifuged at a rotary speed of 400 rpm for 10 minutes. A concentration of the diazepam in the plasma sample was analyzed using LC-MS/MS. A 0.1% formic acid-acetonitrile/deionized water (60/40, v/v) mixed solution was used as a mobile phase, a flow rate was set to 0.25 mL/min, and Xterra®S C_{18} (3.0 x 50 mm, 2.5 micrometers, Waters, USA) was used as a column. The peak detection was performed by a multiple reaction monitoring (MRM) method using a triple-quadrupole mass spectrometry. The ionization was analyzed in a positive mode using an electrospray ionization (ESI) method, and the ion spray temperature was set to 500℃. Protonated molecular ions of the diazepam and the internal standard substance were monitored at m/z 284.9 and 268.0, respectively, using an MRM method, and their product ions were monitored at m/z 154.1 and 155.0, respectively. An area under the plasma concentration-time curve (AUC) from 0 to 4 hours was calculated according to the linear trapezoidal method. The results are listed in the following Table 10 and are shown in FIG. 1.

[81] Table 10

[Table 10]

[Table]

bioavailability of diazepam-containing transnasal administration formulations

	Bioavailability (F,%)
Intravenous injectable formulation	100%
Formulation 1	109%
Formulation 2	82%
Formulation 3	119%
Formulation 4	85%

[82]

[83] Example 6: Pharmacokinetic test of lorazepam-containing nasal formulation in rabbit (Bioavailability test)

[84] Lorazepam was dissolved instead of the diazepam in a solution of formulation 1 so that the lorazepam was present in a content of 9%. Then, this experiment was performed in the same manner as in Example 5. In this case, the lorazepam was set to a concentration of 9%, and was administered at a dose of 1.6 mg/kg. Ativan injection (4mg/mL, Il Dong Pharm. Co., Ltd) was used as the lorazepam in the intravenous injectable formulation, and was administered at a dose of 0.8 mg/kg. Each plasma sample pre-treated with acetonitrile was quantified under the following LC/MS/MS conditions. A 0.1% formic acid-acetonitrile/deionized water (60/40, v/v) mixed solution was used as a mobile phase, a flow rate was set to 0.25 mL/min, and Xterra®MS C_{18} (3.0 x 50 mm, 2.5 micrometers, Waters, USA) was used as a column. The peak detection was performed by a multiple reaction monitoring (MRM) method using a triple-quadrupole mass spectrometry. The ionization was analyzed in a positive mode using an electrospray ionization (ESI) method, and the ion spray temperature was set to 500°C. Protonated molecular ions of the diazepam and the internal standard substance were monitored at m/z 320.9 and 268.0, respectively, using an MRM method, and their product ions were monitored at m/z 275.0 and 155.0, respectively. The results are listed in the following Table 11 and are shown in FIG. 2.

[85] Table 11

[Table 11]

[Table]

bioavailability of lorazepam-containing transnasal administration formulations

	Bioavailability (F,%)
Intravenous injectable formulation	100%
Formulation 1- Lorazepam	33%

[86]

Claims

[1] An anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray-administered, comprising diethylene glycol monoethyl ether and fatty acid ester, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20.

[2] The anticonvulsive pharmaceutical composition of claim 1, wherein the poorly soluble anticonvulsant is at least one selected from the group consisting of diazepam and lorazepam.

[3] The anticonvulsive pharmaceutical composition of claim 2, wherein the poorly soluble anticonvulsant is present in a content of 1 to 20 % by weight, based on the total weight of the pharmaceutical composition.

[4] The anticonvulsive pharmaceutical composition of claim 1, wherein the fatty acid ester is present in a content of at least 30 % by weight, based on the total weight of the pharmaceutical composition.

[5] A pharmaceutical composition, comprising 5 to 20 % by weight of at least one poorly soluble anticonvulsant selected from the group consisting of diazepam and lorazepam, 40 to 60 % by weight of diethylene glycol monoethyl ether, and 35 to 50 % by weight of fatty acid ester, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, methyl laurate, ethyl laurate, and polysorbate 20.

[6] The pharmaceutical composition of claim 5, wherein the fatty acid ester is at least one selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate 20, and polysorbate 20.

[7] An anticonvulsive pharmaceutical composition comprising a poorly soluble anticonvulsant as an active component, which is transnasally spray-administered, comprising diethylene glycol monoethyl ether, fatty acid ester, methylpyrrolidone, water and alcohol.

[8] The anticonvulsive pharmaceutical composition of claim 7, wherein the poorly soluble anticonvulsant is at least one selected from the group consisting of diazepam and lorazepam.

[9] The anticonvulsive pharmaceutical composition of claim 7, wherein the fatty acid ester is selected from the group consisting of caprylocaproyl polyoxylglyceride, isopropyl palmitate, oleoyl polyoxylglyceride, sorbitan monolaurate

20, methyl laurate, ethyl laurate, polysorbate 20 and propylene glycol mono-caprylate.

[10] The anticonvulsive pharmaceutical composition of claim 9, wherein the fatty acid ester comprises methyl laurate.

[11] The anticonvulsive pharmaceutical composition of claim 7, wherein the alcohol is ethanol.

[12] The anticonvulsive pharmaceutical composition of claim 7, wherein the poorly soluble anticonvulsant is present in a content of 1 to 20 % by weight, based on the total weight of the pharmaceutical composition.

[13] The anticonvulsive pharmaceutical composition of claim 7, wherein the pharmaceutical composition has kinetic viscosity of 10 ㎟/sec or less for the transnasal spray-administration.

[14] The anticonvulsive pharmaceutical composition of claim 7, wherein the fatty acid ester is present in a content of at least 30 % by weight, based on the total weight of the pharmaceutical composition.

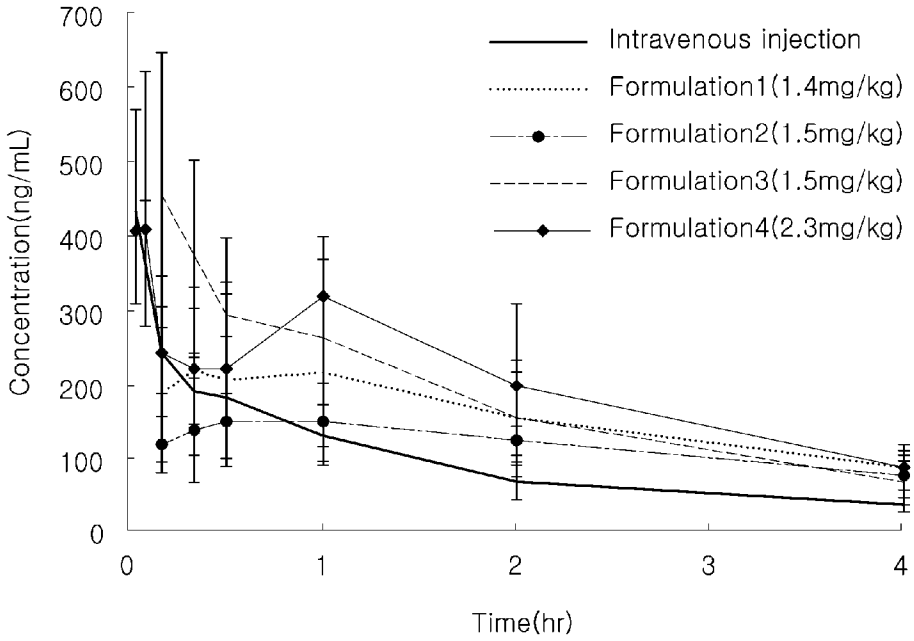
[15] The anticonvulsive pharmaceutical composition of claim 7, comprising 5 to 20 % by weight of at least one poorly soluble anticonvulsant selected from the group consisting of diazepam and lorazepam, 40 to 60 % by weight of diethylene glycol monoethyl ether, 5 to 15 % by weight of methyl laurate, 5 to 30 % by weight of methylpyrrolidone, 1 to 5 % by weight of water, and 5 to 10 % by weight of ethanol.

[16] The anticonvulsive pharmaceutical composition of claim 7, further comprising dimethyl isosorbide.

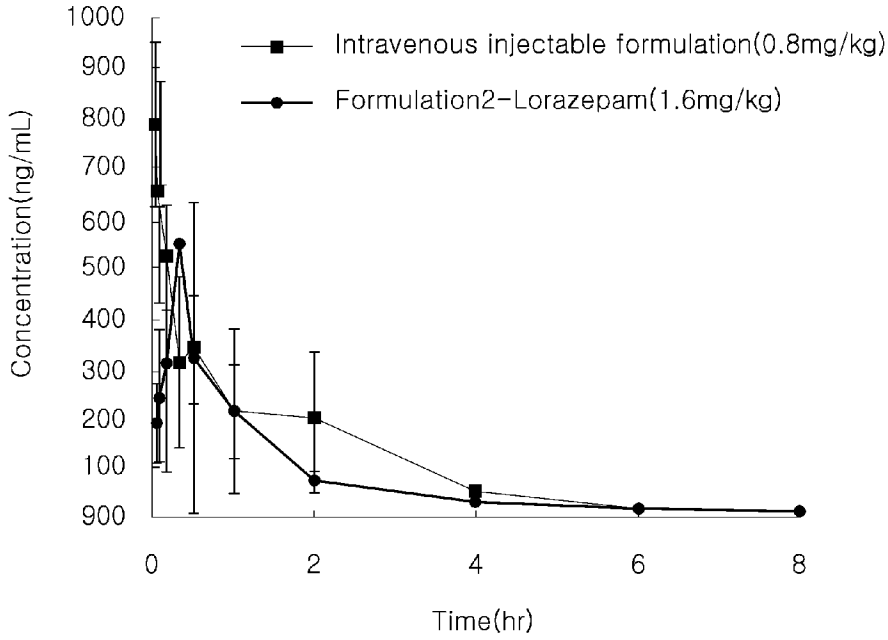
[17] The anticonvulsive pharmaceutical composition of claim 16, wherein the dimethyl isosorbide is present in a content of 5 to 10 % by weight, based on the total weight of the pharmaceutical composition.

[18] A method for treating convulsions, comprising:
transnasally spray-administering to patients suffering from the convulsions a sufficient amount of the pharmaceutical composition defined in any one of claims 1 to 17 to treat the convulsions.

[Fig. 1]



[Fig. 2]



[Fig. 3]

