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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 August 2013 (15.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/119059 A1

(51) International Patent Classification:
A61K 31/661 (2006.01) *A61K 31/675* (2006.01)
A61K 31/66 (2006.01) *A61K 9/08* (2006.01)

(21) International Application Number:
PCT/KR2013/000999

(22) International Filing Date:
7 February 2013 (07.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2012-0012360 7 February 2012 (07.02.2012) KR

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(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, BN, BR, BW, BY, BZ, CA, CH, CL, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

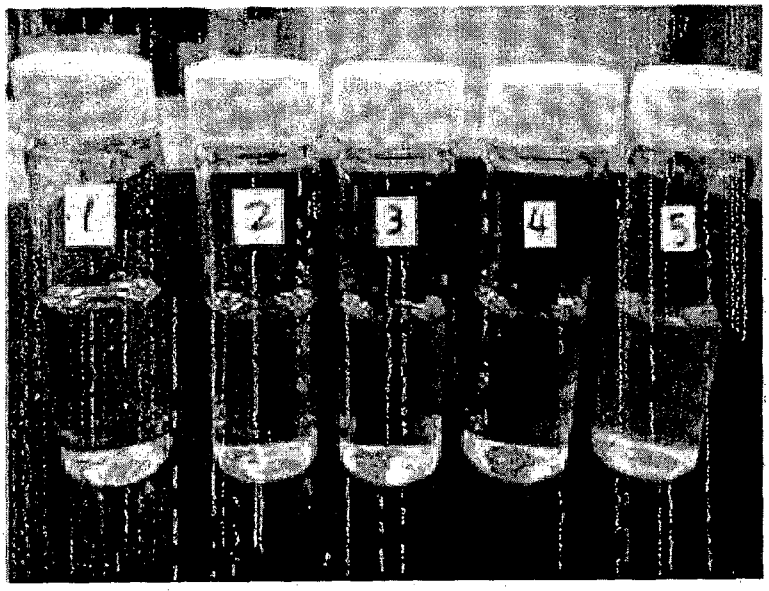
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: INJECTABLE COMPOSITION CONTAINING PHOSPHATIDYLCHOLINE DEVOID OF SODIUM DEOXYCHOLATE AND PREPARING METHOD THEREOF



(57) Abstract: The present invention provides an injectable composition containing phosphatidylcholine comprising phosphatidylcholine; ethanol; propylene glycol and/or benzyl alcohol; polysorbate and/or macrogol 15 hydroxystearate; and a balance of water or water for injection, and a preparing method thereof. An injectable composition of the present invention comprises no sodium deoxycholate which is known as carcinogenic and therefore the more safe injectable composition of phosphatidylcholine can be prepared.

WO 2013/119059 A1

【DESCRIPTION】

【Invention Title】

INJECTABLE COMPOSITION CONTAINING PHOSPHATIDYLCHOLINE DEVOID OF SODIUM DEOXYCHOLATE AND PREPARING METHOD THEREOF

【Technical Field】

<1> The present invention relates to an injectable composition containing phosphatidylcholine devoid of sodium deoxycholate and a preparing method thereof, and more particularly to an injectable composition containing phosphatidylcholine comprising phosphatidylcholine; ethanol; propylene glycol and/or benzyl alcohol; polysorbate and/or macrogol 15 hydroxystearate; and a balance of water or water for injection, and to a preparing method thereof.

<2>

【Background Art】

<3> Phosphatidylcholines are a class of phospholipids that contain choline as a head group. They are widely present in animals, plants, yeasts and fungi, and are also known as lecithin. They are the membrane phospholipids of mammals and are found mainly in brains,nerves, blood cells, egg yolks and the like. In plants, phosphatidylcholines are found in soybeans, sunflower seeds, wheat germs and the like. Phosphatidylcholines generally contain saturated fatty acid at position 1 and unsaturated fatty acid at position 2 of glycerol.

<4>

<5> Normally, liver cells synthesize phospholipids as required, but if liver cells are damaged, they cannot synthesize an increased amount of phospholipids required to restore the membrane structures within a short time.

<6>

<7> Generally, when the synthesis of albumin and coagulation factors decreases, a damagedliver has a significantly reduced ability to synthesize phospholipids, and a significant amount of energy is consumed to produce new phospholipids.

<8>

<9> The loss of phospholipids by liver disease causes damage to liver cell membranes and organelles, which is difficult to restore. In an attempt to prevent this loss, there was developed a method in which high purity phosphatidylcholine is supplied into the body so that it is bound to the membrane structure of damaged liver cells to restore the membrane. When phosphatidylcholine is supplied, the exchange of nutrients and electrolytes across membranes is increased, the activity of phospholipid-dependent enzymes is also increased, and high-energy phosphatidylcholine molecules are bound to liver cells to reduce the burden to supply a large amount of energy required for the production of structural and functional components of membrane systems to the liver. Based on the above facts, injectable formulations containing high-purity phosphatidylcholine have been developed and used for recovery from hepatic coma caused by liver cirrhosis.

<10>

<11> In addition, since it was recently reported that phosphatidylcholine has the effect of decomposing locally accumulated fat, injectable formulations containing phosphatidylcholine have been widely used for local lipolysis for beauty purposes.

<12>

<13> Drugs need to be solubilized before injection. If drugs are injected in a non-solubilized state, they are not easily decomposed into single molecules, and the desired levels thereof in blood cannot be obtained. In addition, because non-solubilized drugs can block blood vessels to cause thrombosis, they are not used as injectable formulations. If drugs form a suspended precipitate without being solubilized when they are injected intravenously, large particles will block blood vessels and affect blood flow in tissue around the blocked blood vessels or damage or stimulate the tissue to cause itching, pain, redness, etc. In severe cases, embolism may also occur.

<14> Phosphatidylcholine is a phospholipid component that is not easily soluble in water-soluble solvents for injection. Thus, sodium deoxycholate is added in order to solubilize phosphatidylcholine.

<15> However, sodium deoxycholate that is the main component of bile acid can cause safety concerns when it is applied to body tissues other than the small intestines. In addition, it may cause colorectal cancer. Thus, it appears that sodium deoxycholate is unsuitable for use as the active ingredient of a solubilizer for a drug for intravenous (or subcutaneous) injection.

<16>

<17> Accordingly, there is an urgent need for the development of a phosphatidylcholine-containing injectable composition which contains no sodium deoxycholate and in which phosphatidylcholine is solubilized so as to be injectable intravenously (or subcutaneously).

<18>

【Disclosure】

【Technical Problem】

<19> Accordingly, the present inventors have conducted studies on an injectable composition which comprises no sodium deoxycholate and in which phosphatidylcholine is stably solubilized. As a result, the present inventors have found that phosphatidylcholine is solubilized by a combination of some solubilizers and solubilization aids without sodium deoxycholate, thereby completing the present invention.

<20>

<21> Therefore, it is an object of the present invention to provide an injectable composition containing phosphatidylcholine consisting of:

<22> 2-10% (w/v) of phosphatidylcholine

<23> 5-40% (w/v) of ethanol

<24> 2-20 % (w/v) of one or more selected from the group consisting of propylene glycol and benzyl alcohol

<25> 1-30% (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate and

<26> a balance of water or water for injection.

<27>

<28> Another object of the present invention is to provide a method for

preparing an injectable composition containing phosphatidylcholine comprising the steps of:

<29> (a) adding phosphatidylcholine and one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to ethanol;

<30> (b) adding one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a); and

<31> (c) adding water or water for injection to the mixture of step(b) until a predetermined total volume is reached.

<32>

【Technical Solution】

<33> To acheive the above object, the present invention provides an injectable composition containing phosphatidylcholine consisting of:

<34> 2-10% (w/v) of phosphatidylcholine,

<35> 5-40% (w/v) of ethanol,

<36> 2-20 % (w/v) of one or more selected from the group consisting of propylene glycol and benzyl alcohol,

<37> 1-30% (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate and

<38> a balance of water or water for injection.

<39>

<40> To acheive another object, the present invention provides a method for preparing an injectable composition containing phosphatidylcholine comprising the steps of:

<41> (a) adding phosphatidylcholine and one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to ethanol;

<42> (b) adding one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a); and

<43> (c) adding water or water for injection to the mixture of step(b)until a predetermined total volume is reached.

<44>

<45>

<46> Hereinafter, the present invention will be described in detail.

<47> An injectable composition of the present invention is characterized by comprising:

<48> 2-10% (w/v) of phosphatidylcholine,

<49> 5-40% (w/v) of ethanol,

<50> 2-20 % (w/v) of one or more selected from the group consisting of propylene glycol and benzyl alcohol,

<51> 1-30% (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate and

<52> a balance of water or water for injection.

<53>

<54> An injectable formulation is obtained by dissolving an active ingredient and other additives in distilled water for injection, filtering the solution through a bacterial filter to remove bacterial cells, and filling the filtered solution into a vial in an aseptic condition, and then sealing the vial. Phosphatidylcholine that is contained in the injectable composition according to the present invention is also known as lecithin and is the most typical phospholipid. It accounts for about 70% of total phospholipids in yolk eggs and about 60% of total phospholipids in human serum.

<55> Soybean lecithin contains a component consisting of two fatty acids and linoleic acid, unlike other lecithins, and thus has the effect of improving lipid metabolism. In the composition of the present invention, the concentration of phosphatidylcholine is preferably 2-10% (w/v).

<56> In addition, ethanol that is contained in the injectable composition according to the present invention is ethane with a hydrogen molecule replaced by a hydroxyl radical. The concentration of ethanol in the composition according to the present invention is preferably 5-40% (w/v).

<57> In addition, propylene glycol that is contained in the injectable composition according to the present invention is a colorless transparent liquid similar to glycerin and is generally used as a preservative, because it has moisture-absorbing and moisture-holding properties and preservative properties. Moreover, benzyl alcohol that is contained in the injectable

composition according to the present invention is one of aromatic alcohols, which is a colorless transparent liquid. It has a peculiar fragrance and a sharp taste and is generally used as a dissolution agent, an extraction agent, a volatilization inhibitor, a food spice and the like. The concentration of propylene glycol and/or benzyl alcohol in the composition according to the present invention is preferably 2-20% (w/v).

<58> In addition, macrogol 15 hydroxystearate that is contained in the injectable composition according to the present invention is generally used as a nonionic surfactant, has good chemical stability and low toxicity and easily dissolves in water, ethanol and 2-propanol. Further, polysorbate that is contained in the injectable composition according to the present invention is a polyoxyethylene higher aliphatic alcohol consisting of ethylene oxide bonded to sorbitan fatty acid ester and is a kind of nonionic surfactant. It is divided, according to the number of polyoxyethylene groups and the kind of fatty acid, into polysorbate 20 (monolauric acid), 40 (monopalmitic acid), 60 (monostearic acid), 65 (tristearic acid) and 80 (mono-oleic acid).Among them, polysorbate 80 is preferably used in the present invention. The concentration of polysorbate and/or macrogol in the composition according to the present invention is preferably 1-30% (w/v).

<59> In addition, the water for injection that is contained in the injectable composition according to the present invention is distilled water made to dissolve a solid formulation or dilute a water-soluble formulation. Specific examples thereof include glucose injection, xylitol injection, D-mannitol injection, fructose injection, physiological saline, dextran 40 injection, dextran 70 injection, amino acid injection, Ringer solution, lactic acid-Ringer solution or the like.

<60> The injectable composition of the present invention is a phosphatidylcholine-containing injectable composition containing no sodium deoxycholate and does not cause the risk of colorectal cancer.

<61> The above-described inventive phosphatidylcholine-containing injectable composition, which comprises phosphatidylcholine, ethanol, propylene glycol and/or benzyl alcohol, polysorbate and/or macrogol 15 hydroxystearate, and a

balance of water or water for injection, has not been reported before the present invention.

<62>

<63> Meanwhile, a method of the present invention is characterized by comprising the steps of:

<64> (a) adding phosphatidylcholine and one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to ethanol;

<65> (b) adding one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a); and

<66> (c) adding water or water for injection to the mixture of step(b)until a predetermined total volume is reached.

<67>

<68> The preparing method of the injectable composition could be explain step by step as follows:

<69>

<70> (a) step : adding (and mixing (suspending or blending)) phosphatidylcholine and one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to ethanol

<71> The ingredients of phosphatidylcholine, polysorbate and macrogol 15 hydroxystearate in step (a) are same as the above-mentioned. Preferably, after mixing the ingredients of step (a), the mixture is stirred until a clear solution is formed .

<72> The (a) step may comprise adding 2-10% (w/v) of phosphatidylcholine and 2-20 % (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to 5-40% (w/v) of ethanol.

<73>

<74> (b) step : adding (and mixing (suspending or blending)) one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a)

<75> The ingredients of propylene glycol and benzyl alcohol, and water for injection in step (b) are same as the above-mentioned.

<76> The (b) step may comprise adding 1-30% (w/v) of one or more selected

from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a).

<77>

<78> (c) step : adding (and mixing (suspending or blending)) water or water for injection to the mixture of step (b)until a predetermined total volume is reached

<79> Preferably, after adding water or water for injection of step (c), the resulting solution is homogenized.

<80>

<81> In one example of the present invention, in order to find an injectable composition capable of solubilizing phosphatidylcholine without having to use sodium deoxycholate, unlike conventional injectable compositions containing phosphatidylcholine, the abilities of various combinations of additives for intravenous injection to solubilize phospholipids were evaluated.

<82> As a result, it was shown that one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate and one or more selected from the group consisting of propylene glycol and benzyl alcohol are suitable as solubilizers (see Example 1).

<83> In another example of the present invention, using the composition found to be the most excellent combination in the above-described example (Example 1), the degree of solubilization was measured while changing the concentrations of the components of the composition.

<84> As a result, it was shown that other solubilizers (PEG 400, urea, β-cyclodextrin, sorbitol, span 80, poloxamer 188, glycerol, etc.) have no significant effect.

<85> Accordingly, the injectable composition of phosphatidylcholine, which comprises phosphatidylcholine, ethanol, propylene glycol and/or benzyl alcohol, polysorbate and/or macrogol 15 hydroxystearate, and a balance of water or water for injection, can be used as an injectable composition having an excellent ability to solubilize phosphatidylcholine without having to use sodium deoxycholate.

<86> The method for administration of the injectable composition of the

present invention is not specifically limited, but can be suitably selected in view of the severity of disease, and the patient's age, sex and other conditions. The route for administration of the injectable composition of the present invention is not specifically limited, but is preferably subcutaneous injection, transdermal injection, intravenous injection, intramuscular injection, intraperitoneal injection or the like.

<87>

【Advantageous Effects】

<88> Accordingly, the present invention provides an injectable composition of phosphatidylcholine comprising phosphatidylcholine; ethanol; propylene glycol and/or benzyl alcohol; polysorbate and/or macrogol 15 hydroxystearate; and a balance of water or water for injection. An injectable composition of the present invention comprises no sodium deoxycholate and phosphatidylcholine is stably solubilized in thereof. As a result, the present invention provides more safe injectable composition of phosphatidylcholine.

<89>

【Description of Drawings】

<90> FIG. 1 shows comparision of the status of compositions for solubilization of phosphatidylcholine and the numbers in vial refers the test numbers of the Table 2 of the Example 2.

<91>

【Mode for Invention】

<92> Hereinafter, the present invention will be described in detail with reference to following Examples.

<93> However, the following Examples are only for illustrative purposes and are not intended to limit the scope of the invention.

<94>

<95> **<Example 1>**

<96> **Experiment on solubilization of phosphatidylcholine using various components of composition for solubilization**

<97>

<98> In order to find an injectable composition capable of solubilizing phosphatidylcholine without having to use sodium deoxycholate, unlike conventional injectable compositions containing phosphatidylcholine, the abilities of various combinations of additives for intravenous injection to solubilize phospholipids were evaluated.

<99> Phosphatidylcholine, polysorbate 80 and ethanol were mixed with each other in the amounts shown in Table 1 below, and the mixture was stirred at 300 rpm at 30 ℃ for 30 minutes in a closed space under light-free conditions.

<100> The phosphatidylcholine was purchased from Lipoid GmbH (Germany) (Cat. No. 368202, Model: PHOSPHOLIPON® 90G).

<101> To the mixture, 45 mg of benzyl alcohol was added, and other various solubilizers were added. Water for injection was added thereto until a total volume of 5 ml was reached. The resulting solution was stirred at 300 rpm at 30 ℃ for 3 hours in a closed space under light-free conditions, thereby preparing an injectable composition.

<102> Visual observation was carried out to determine whether the above-prepared injectable composition undergoes phenomena, including precipitation, suspension and phase separation, and is transparent. As a control, a conventional injectable formulation containing sodium deoxycholate (5 mg injectable formulation comprising 250 mg phosphatidylcholine, 120 mg sodium deoxycholate, 12 mg sodium chloride, 45 mg benzyl alcohol, 10 mg ethanol and a balance of water for injection) was used.

<103> Observation results were expressed as follows: (+): there are no phenomena, including precipitation, suspension and phase separation, and transparency is equal to or higher than that of the control; and (-): solubilization is insufficient, or transparency is lower than that of the control group.

<104> As a result, as can be seen in Table 1 below, when PEG 400, urea, β-cyclodextrin, sorbitol, span 80, poloxamer 188 and glycerol were added, solubilization was insufficient, and when propylene glycol or macrogol 15 hydroxystearate was added as an additive, the degree of solubilization was

similar to that of the control, and the composition was transparent. Thus, it was determined that a combination of phosphatidylcholine, ethanol, benzyl alcohol, polysorbate, propylene glycol or macrogol 15 hydroxystearate, and water for injection can be used as a phosphatidylcholine-containing injectable composition free of sodium deoxycholate.

<105>

<106> 【Table 1】

<107> Solubility according to additives

<108>

No.	1	2	3	4	5
essential phospholipid material	250mg	250mg	250mg	250mg	250mg
polysorbate 80	500mg	500mg	500mg	500mg	500mg
ethanol	500mg	500mg	500mg	500mg	500mg
benzyl alcohol	45mg	45mg	45mg	45mg	45mg
other additives	propylene glycol 500mg	PEG 400 500mg	urea 500mg	β-cyclodextrin 100mg	sorbitol 500mg
water for injection	remainder	remainder	remainder	remainder	remainder
status	+	-	-	-	-

<109>

<111>

No.	6	7	8	9	
essential phospholipid material	250mg	250mg	250mg	250mg	
polysorbate 80	500mg	500mg	500mg	500mg	
ethanol	500mg	500mg	500mg	500mg	
benzyl alcohol	45mg	45mg	45mg	45mg	
other additives	span 80 500mg	poloxamer 188 100mg	glycerol 500mg	Macrogol 15 Hydroxystearate	
water for injection	remainder	remainder	remainder	remainder	
status	-	-	-	+	

<112>

<113>

<114> **<Example 2>**

Experiment on solubilization of phosphatidylcholine using various

concentrations of components of composition for solubilization

<115> The components selected in Example 1 were combined with each other so as to have various components and concentrations, and the conditions in which an optimal injectable composition for solubilization is obtained were determined.

<118> Phosphatidylcholine, polysorbate 80 and/or macrogol 15 hydroxystearate, and ethanol were mixed with each other in the amounts shown in Table 2 below, and the mixture was stirred at 300 rpm at 30 ℃or 30 minutes in a closed space under light-free conditions.

<119> To the mixture, propylene glycol and/or benzyl alcohol was added in the amounts shown in Table 2 below, and water for injection was added thereto until a total volume of 5 ml was reached. The resulting solution was stirred at 300 rpm at 30 ℃ for 3 hours in a closed space under light-free conditions, thereby preparing an injectable composition.

<120> Visual observation was carried out to determine whether the above-prepared injectable composition undergoes phenomena, including precipitation, suspension and phase separation, and is transparent. As a control, a conventional injectable formulation containing sodium deoxycholate (5 mg injectable formulation comprising 250 mg phosphatidylcholine, 120 mg sodium deoxycholate, 12 mg sodium chloride, 45 mg benzyl alcohol, 10 mg ethanol and a balance of water for injection) was used.

<121> Observation results were expressed as follows: (+): there are no phenomena, including precipitation, suspension and phase separation, and transparency is equal to or higher than that of the control; and (-): solubilization is insufficient, or transparency is lower than that of the control group.

<122>

<123> As a result, as can be seen in Table 2 below, it was found that, when propylene glycoland benzyl alcohol were not added, the solubilizing effect was insufficient, and when propylene glycol and/or benzyl alcohol, and polysorbate and/or macrogol 15 hydroxystearatewere added as additives, the

degree of solubilization was sufficient, similar to that of the control, and the composition was transparent. Thus, it determined found that a combination of phosphatidylcholine, ethanol, propylene glycol and/or benzyl alcohol, and polysorbate and/or macrogol 15 hydroxystearate can be used as a phosphatidylcholine-containing injectable composition free of sodium deoxycholate.

<124>

<125> 【Table 2】

<126> Solubility according to the concentration of additives

<127>

Test No.	1	2	3	4	5
essential phospholipid material	287.5mg	287.5mg	287.5mg	287.5mg	287.5mg
propyleneglycol			500mg	500mg	
benzyl alcohol	200mg	100mg			
Polysorbate 80(Tween80)	120mg	200mg		600mg	600mg
Ethanol	1500mg	1500mg	1000mg	500mg	500mg
Macrogol 15 Hydroxystearate			500mg	500mg	500mg
Water for injection	remainder	remainder	remainder	remainder	remainder
Total	5ml	5ml	5ml	5ml	5ml
status	+	+	+	+	-

【Industrial Applicability】

<128> As can be seen foregoing, the present invention provides an injectable composition containing phosphatidylcholine comprising phosphatidylcholine; ethanol; propylene glycol and/or benzyl alcohol; polysorbate and/or macrogol 15 hydroxystearate; and a balance of water or water for injection, and a preparing method thereof. An injectable composition of the present invention comprises no sodium deoxycholate and phosphatidylcholine is stably solubilized in thereof. As a result, the present invention provides more safe injectable composition of phosphatidylcholine.

<129>

【CLAIMS】

【Claim 1】

<131> An injectable composition containing phosphatidylcholine consisting of:

<132> 2-10% (w/v) of phosphatidylcholine

<133> 5-40% (w/v) of ethanol

<134> 2-20 % (w/v) of one or more selected from the group consisting of propylene glycol and benzyl alcohol

<135> 1-30% (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate and

<136> a balance of water or water for injection.

<137>

【Claim 2】

<138> A method for preparing an injectable composition containing phosphatidylcholine comprising the steps of:

<139> (a) adding phosphatidylcholine and one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to ethanol;

<140> (b) adding one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a); and

<141> (c) adding water or water for injection to the mixture of step(b) until a predetermined total volume is reached.

<142>

【Claim 3】

<143> The method of claim 2, said (a) step comprises adding 2-10% (w/v) of phosphatidylcholine and 2-20 % (w/v) of one or more selected from the group consisting of polysorbate and macrogol 15 hydroxystearate to 5-40% (w/v) of ethanol.

<144>

【Claim 4】

<145> The method of claim 2, said (b) step comprises adding 1-30% (w/v) of one or more selected from the group consisting of propylene glycol and benzyl alcohol to the mixture of step (a).

【DRAWINGS】

【Figure 1】



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/000999

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/661(2006.01)i, A61K 31/66(2006.01)i, A61K 31/675(2006.01)i, A61K 9/08(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/661; A61K 9/22; A61K 31/685; A61K 47/28; A61K 31/66; A61K 9/08; A61K 31/575

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: phosphatidylcholine, ethanol, propylene glycol, benzyl alcohol, polysorbate, macrogol 15hydroxystearate, injection, injectable

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KR 10-2004-0108567 A (DOOSAN CORPORATION) 24 December 2004 See claims and example 4	1-4
A	KR 10-2007-0110351 A (LOS ANGELES BIOMEDICAL RESEARCH INSTITUTE AT HARBOR-UC LA MEDICAL CENTER et al.) 16 November 2007 See claims 1 and 11	1-4
A	JP 2007-509085 A (AVENTIS PHARMA DEUTSCHLAND GMBH et al.) 12 April 2007 See claims	1-4
A	WO 2011-024354 A1 (MEDRX CO., LTD. et al.) 03 March 2011 See claims	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2013 (31.05.2013)	**31 May 2013 (31.05.2013)**

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Form PCT/ISA/210 (second sheet) (July 2009)

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International application No.
PCT/KR2013/000999

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(12)发明专利申请

(10)申请公布号 CN 104080460 A
(43)申请公布日 2014.10.01

(21)申请号 201380007280.2
(22)申请日 2013.02.07
(30)优先权数据
10-2012-0012360 2012.02.07 KR
(85)PCT国际申请进入国家阶段日
2014.07.30
(86)PCT国际申请的申请数据
PCT/KR2013/000999 2013.02.07
(87)PCT国际申请的公布数据
WO2013/119059 EN 2013.08.15
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(51)Int.Cl.
A61K 31/661(2006.01)
A61K 31/66(2006.01)
A61K 31/675(2006.01)
A61K 9/08(2006.01)

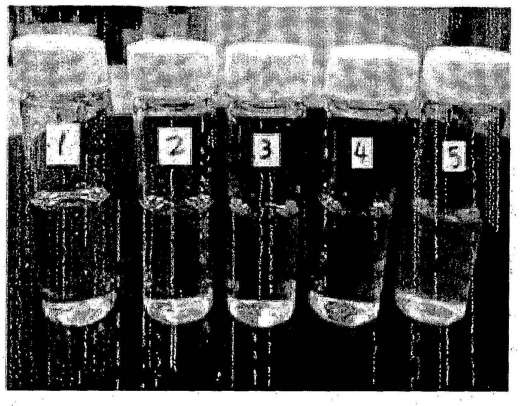
权利要求书1页 说明书7页 附图1页

(54)发明名称

不含脱氧胆酸钠的含磷脂酰胆碱的可注射组合物及其制备方法

(57)摘要

本发明提供了一种含有磷脂酰胆碱的可注射组合物及其制备方法，所述组合物包含：磷脂酰胆碱；乙醇；丙二醇和/或苄醇；聚山梨醇酯和/或聚乙二醇15羟基硬脂酸酯；以及余量的水或注射用水。本发明的可注射组合物不包含已知为致癌物的脱氧胆酸钠，并且因此可制备更安全的磷脂酰胆碱可注射组合物。



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1. 一种含有磷脂酰胆碱的可注射组合物，所述可注射组合物由以下物质组成：

2%～10%(w/v)的磷脂酰胆碱；

5%～40%(w/v)的乙醇；

2%～20%(w/v)的选自由丙二醇和苄醇组成的组的一种或多种；

1%～30%(w/v)的选自由聚山梨醇酯和聚乙二醇15羟基硬脂酸酯组成的组的一种或多种；以及

余量的水或注射用水。

2. 一种制备含有磷脂酰胆碱的可注射组合物的方法，所述方法包括以下步骤：

(a)在乙醇中添加磷脂酰胆碱以及选自由聚山梨醇酯和聚乙二醇15羟基硬脂酸酯组成的组的一种或多种；

(b)在步骤(a)的混合物中添加选自由丙二醇和苄醇组成的组的一种或多种；和

(c)在步骤(b)的混合物中添加水或注射用水直至达到预定的总体积。

3. 如权利要求2所述的方法，所述(a)步骤包括在5%～40%(w/v)的乙醇中添加2%～10%(w/v)的磷脂酰胆碱以及2%～20%(w/v)的选自由聚山梨醇酯和聚乙二醇15羟基硬脂酸酯组成的组的一种或多种。

4. 如权利要求2所述的方法，所述(b)步骤包括在步骤(a)的混合物中添加1%～30%(w/v)的选自由丙二醇和苄醇组成的组的一种或多种。

不含脱氧胆酸钠的含磷脂酰胆碱的可注射组合物及其制备方法

技术领域

[0001] 本发明涉及一种不含脱氧胆酸钠的含磷脂酰胆碱的可注射组合物及其制备方法，并且更具体地涉及一种含有磷脂酰胆碱的可注射组合物及其制备方法，所述组合物包含：磷脂酰胆碱；乙醇；丙二醇和/或苄醇；聚山梨醇酯和/或聚乙二醇15羟基硬脂酸酯；以及余量的水或注射用水。

背景技术

[0002] 磷脂酰胆碱是含有胆碱作为头基的一类磷脂。它们广泛地存在于动物、植物、酵母和真菌中，又称为卵磷脂。它们是哺乳动物的膜磷脂，主要出现在大脑、神经、血细胞、卵黄等中。在植物中，磷脂酰胆碱出现在大豆、向日葵籽、麦芽等中。磷脂酰胆碱通常含有在甘油的1位的饱和脂肪酸以及在甘油的2位的不饱和脂肪酸。

[0003] 通常，肝细胞根据需要合成磷脂，但如果肝细胞受损，则其不能合成在短时间内恢复膜结构所需的增量的磷脂。

[0004] 一般而言，当白蛋白和凝结因子的合成减少时，受损的肝脏合成磷脂的能力显著降低，并且消耗大量能量以产生新磷脂。

[0005] 肝脏疾病所致的磷脂损失对肝细胞膜和细胞器造成难以恢复的损伤。为了防止这种损失，开发出了一种方法：将高纯度的磷脂酰胆碱供应至体内从而使其与受损的肝细胞的膜结构结合以使膜恢复。当供应了磷脂酰胆碱时，营养物质和电解质的跨膜交换增加，磷脂依赖性酶的活性也增加，并且高能磷脂酰胆碱分子与肝细胞结合，从而减轻了向肝脏供应产生膜系统的结构和功能组分所需的大量能量的负担。基于以上事实，已开发出了含有高纯度磷脂酰胆碱的可注射制剂并且用于从肝硬化引起的肝性昏迷中恢复。

[0006] 另外，由于最近报道了磷脂酰胆碱具有分解局部累积的脂肪的效果，所以出于美容目的，已将含有磷脂酰胆碱的可注射制剂广泛用于局部脂解。

[0007] 在注射之前，药物需要是增溶的(solubilized)。如果药物以非增溶的状态注射，则其不易分解为单个分子，并且无法获得其在血液中的期望水平。另外，由于非增溶的药物能够阻塞血管造成血栓，所以不将其用作可注射制剂。如果在静脉内注射药物时其在未增溶的情况下形成悬浮的沉淀物，则大颗粒会阻塞血管并且影响被阻塞血管周围的组织中的血液流动，或者损害或刺激该组织以造成瘙痒、疼痛、泛红等。在严重的情况下，还可能发生栓塞。

[0008] 磷脂酰胆碱是不易溶于注射用水溶性溶剂的磷脂组分。因此，添加脱氧胆酸钠以将磷脂酰胆碱增溶。

[0009] 然而，当将作为胆汁酸主要组分的脱氧胆酸钠施用于小肠以外的身体组织时，其可能引起安全问题。另外，其可能引起结肠直肠癌。因此，脱氧胆酸钠看似不宜用作静脉内(或皮下)注射用药物的增溶剂的活性成分。

[0010] 因此，迫切需要开发出不含脱氧胆酸钠的含磷脂酰胆碱的可注射组合物，其中磷

脂酰胆碱是增溶的，以便能够静脉内（或皮下）注射。

发明内容

[0011] [技术问题]

[0012] 因此，本发明人对不包含脱氧胆酸钠并且其中磷脂酰胆碱得到稳定增溶的可注射组合物进行了研究。结果，本发明人发现了磷脂酰胆碱在无脱氧胆酸钠的情况下通过一些增溶剂和增溶助剂的组合而得到增溶，由此完成了本发明。

[0013] 因此，本发明的目的是提供一种含磷脂酰胆碱的可注射组合物，其由以下物质组成：

[0014] 2～10％ (w/v) 的磷脂酰胆碱；

[0015] 5～40％ (w/v) 的乙醇；

[0016] 2～20％ (w/v) 的选自由丙二醇和苄醇组成的组的一种或多种；

[0017] 1～30％ (w/v) 的选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种；以及

[0018] 余量的水或注射用水。

[0019] 本发明的另一个目的是提供一种制备含有磷脂酰胆碱的可注射组合物的方法，其包括以下步骤：

[0020] (a) 在乙醇中添加磷脂酰胆碱以及选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种；

[0021] (b) 在步骤 (a) 的混合物中添加选自由丙二醇和苄醇组成的组的一种或多种；以及

[0022] (c) 在步骤 (b) 的混合物中添加水或注射用水直至达到预定的总体积。

[0023] [技术方案]

[0024] 为了实现以上目的，本发明提供了一种含磷脂酰胆碱的可注射组合物，其由以下物质组成：

[0025] 2～10％ (w/v) 的磷脂酰胆碱；

[0026] 5～40％ (w/v) 的乙醇；

[0027] 2～20％ (w/v) 的选自由丙二醇和苄醇组成的组的一种或多种；

[0028] 1～30％ (w/v) 的选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种；以及

[0029] 余量的水或注射用水。

[0030] 为了实现另一个目的，本发明提供了一种制备含有磷脂酰胆碱的可注射组合物的方法，其包括以下步骤：

[0031] (a) 在乙醇中添加磷脂酰胆碱以及选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种；

[0032] (b) 在步骤 (a) 的混合物中添加选自由丙二醇和苄醇组成的组的一种或多种；以及

[0033] (c) 在步骤 (b) 的混合物中添加水或注射用水直至达到预定的总体积。

[0034] 在下文中，将详细描述本发明。

[0035] 本发明的可注射组合物的特征在于包括：

[0036] 2～10％(w/v)的磷脂酰胆碱；

[0037] 5～40％(w/v)的乙醇；

[0038] 2～20％(w/v)的选自由丙二醇和苄醇组成的组的一种或多种；

[0039] 1～30％(w/v)的选自由聚山梨醇酯和聚乙二醇15羟基硬脂酸酯组成的组的一种或多种；以及

[0040] 余量的水或注射用水。

[0041] 可注射制剂通过以下方式获得：将活性成分和其它添加剂溶解在注射用蒸馏水中，通过细菌滤过器过滤该溶液以去除细菌细胞，并且在无菌条件下将过滤的溶液填充到小瓶中，并且随后将小瓶密封。本发明的可注射组合物中所含的磷脂酰胆碱也称为卵磷脂，并且是最常见的磷脂。其占卵黄中总磷脂的约70％，占人血清中总磷脂的约60％。

[0042] 不同于其它卵磷脂，大豆卵磷脂含有由两种脂肪酸和亚油酸组成的组分，并且由此具有改进脂代谢的效果。在本发明的组合物中，磷脂酰胆碱的浓度优选为2％～10％(w/v)。

[0043] 另外，本发明的可注射组合物中所含的乙醇是氢原子被羟基替代了的乙烷。本发明的组合物中的乙醇的浓度优选为5％～40％(w/v)。

[0044] 另外，本发明的可注射组合物中所含的丙二醇是类似于甘油的无色透明液体，一般用作防腐剂，因为其具有水分吸收和水分保持特性以及防腐性。此外，本发明的可注射组合物中所含的苄醇是一种芳族醇，其是无色透明液体。其具有独特的香味和辛辣味，并且一般用作溶解剂、萃取剂、挥发抑制剂、食物调味料等。本发明的组合物中的丙二醇和/或苄醇的浓度优选为2％～20％(w/v)。

[0045] 另外，本发明的可注射组合物中所含的聚乙二醇15羟基硬脂酸酯一般用作非离子型表面活性剂，其具有良好的化学稳定性和低毒性，并且易溶于水、乙醇和2-丙醇中。此外，本发明的可注射组合物中所含的聚山梨醇酯是一种聚氧化乙烯高级脂肪族醇，由键合有氧化乙烯的山梨聚糖脂肪酸酯组成，是一种非离子型表面活性剂。根据聚氧化乙烯基团的数量和脂肪酸的种类，其分为聚山梨醇酯20(单月桂酸)、40(单棕榈酸)、60(单硬脂酸)、65(三硬脂酸)和80(单油酸)。其中，本发明中优选使用聚山梨醇酯80。本发明的组合物中的聚山梨醇酯和/或聚乙二醇的浓度优选为1％～30％(w/v)。

[0046] 另外，本发明的可注射组合物中所含的注射用水是蒸馏水，用来溶解固体制剂或稀释水溶性制剂。其具体实例包括葡萄糖注射液、木糖醇注射液、D-甘露醇注射液、果糖注射液、生理盐水、右旋糖酐40注射液、右旋糖酐70注射液、氨基酸注射液、林格液或乳酸-林格液等。

[0047] 本发明的可注射组合物是一种不含脱氧胆酸钠的含磷脂酰胆碱的可注射组合物，其不引起结肠直肠癌的风险。

[0048] 上述发明的含磷脂酰胆碱的可注射组合物(其包含磷脂酰胆碱、乙醇、丙二醇和/或苄醇、聚山梨醇酯和/或聚乙二醇15羟基硬脂酸酯、以及余量的水或注射用水)在本发明之前尚未报道过。

[0049] 同时，本发明的方法特征在于包括以下步骤：

[0050] (a)在乙醇中添加磷脂酰胆碱以及选自由聚山梨醇酯和聚乙二醇15羟基硬脂酸

酯组成的组的一种或多种；

[0051] (b) 在步骤 (a) 的混合物中添加选自由丙二醇和苄醇组成的组的一种或多种；以及

[0052] (c) 在步骤 (b) 的混合物中添加水或注射用水直至达到预定的总体积。

[0053] 所述可注射组合物的制备方法可逐步地如下解释：

[0054] (a) 步骤：在乙醇中添加（和混合（悬浮或掺合））磷脂酰胆碱以及选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种

[0055] 步骤 (a) 中的磷脂酰胆碱、聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯的成分与上文所述的相同。优选地，在将步骤 (a) 的各成分混合之后，搅拌混合物直至形成澄清溶液。

[0056] (a) 步骤可以包括在 5％～ 40％ (w/v) 的乙醇中添加 2％～ 10％ (w/v) 的磷脂酰胆碱以及 2％～ 20％ (w/v) 的选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种。

[0057] (b) 步骤：在步骤 (a) 的混合物中添加（和混合（悬浮或掺合））选自由丙二醇和苄醇组成的组的一种或多种

[0058] 步骤 (b) 中的丙二醇和苄醇的成分与上文所述的相同。

[0059] (b) 步骤可以包括在步骤 (a) 的混合物中添加 1％～ 30％ (w/v) 的选自由丙二醇和苄醇组成的组的一种或多种。

[0060] (c) 步骤：在步骤 (b) 的混合物中添加（和混合（悬浮或掺合））水或注射用水直至达到预定的总体积

[0061] 优选的是，在添加步骤 (c) 的水或注射用水之后，将所得溶液均化。

[0062] 在本发明的一个实施例中，为了找到不同于常规的含磷脂酰胆碱可注射组合物的不必使用脱氧胆酸钠就能够将磷脂酰胆碱增溶的可注射组合物，评估了静脉内注射用添加剂的各种组合的磷脂增溶能力。

[0063] 结果显示，适合作为增溶剂的是选自由聚山梨醇酯和聚乙二醇 15 羟基硬脂酸酯组成的组的一种或多种和选自由丙二醇和苄醇组成的组的一种或多种（见实施例 1）。

[0064] 在本发明的另一个实施例中，利用在上述实施例（实施例 1）中发现的最优组合的组合物，在改变所述组合物的各组分的浓度的情况下测量了增溶程度。

[0065] 结果显示，其它增溶剂 (PEG 400、尿素、β－环糊精、山梨醇、司盘 80、泊咯沙姆 188 和甘油等）没有显著的效果。

[0066] 因此，包含磷脂酰胆碱、乙醇、丙二醇和／或苄醇、聚山梨醇酯和／或聚乙二醇 15 羟基硬脂酸酯、以及余量的水或注射用水的磷脂酰胆碱可注射组合物可用作具有不必使用脱氧胆酸钠就能将磷脂酰胆碱增溶的优异能力的可注射组合物。

[0067] 对本发明的可注射组合物的施用方法没有特别限制，但可鉴于疾病严重性和患者的年龄、性别及其它状况来适当选择。对本发明的可注射组合物的施用途径没有特别限制，但优选为皮下注射、经皮注射、静脉内注射、肌内注射或腹膜内注射等。

[0068] [有益效果]

[0069] 因此，本发明提供了一种磷脂酰胆碱可注射组合物，其包含：磷脂酰胆碱；乙醇；丙二醇和／或苄醇；聚山梨醇酯和／或聚乙二醇 15 羟基硬脂酸酯；以及余量的水或注射用水。本发明的可注射组合物不包含脱氧胆酸钠，并且磷脂酰胆碱在其中得到稳定增溶。因

此，本发明可提供更安全的磷脂酰胆碱可注射组合物。

附图说明

[0070] 图 1 显示了用于增溶磷脂酰胆碱的组合物的状态对比，并且小瓶中的数字指实施例 2 的表 2 的测试编号。

具体实施方式

[0071] 在下文中，将参照以下实施例详细描述本发明。

[0072] 然而，以下实施例仅出于说明的目的而并非意欲限制本发明的范围。

[0073] < 实施例 1>

[0074] 利用各种增溶用组合物组分对磷脂酰胆碱的增溶作用进行测试

[0075] 为了找到不同于常规的含磷脂酰胆碱可注射组合物的不必使用脱氧胆酸钠就能够将磷脂酰胆碱增溶的可注射组合物，评估了静脉内注射用添加剂的各种组合的磷脂增溶能力。

[0076] 按照下表 1 中所示的量将磷脂酰胆碱、聚山梨醇酯 80 和乙醇彼此混合，并且在无光条件下于封闭空间内将该混合物在 30℃下以 300rpm 搅拌 30 分钟。

[0077] 磷脂酰胆碱购自 Lipoid GmbH(德国)(目录号 368202，型号 :PHOSPHOLIPON® 90G)。

[0078] 在所述混合物中添加 45mg 苄醇，并且添加其它各种增溶剂。向其添加注射用水直至达到 5ml 的总体积。在无光条件下于封闭空间内将所得溶液在 30℃下以 300rpm 搅拌 3 小时，从而制得可注射组合物。

[0079] 进行目视观察以确定以上制备的可注射组合物是否经历包括沉淀、悬浮和相分离在内的现象，以及是否透明。作为对照，使用含脱氧胆酸钠的常规可注射制剂 (5mg 可注射制剂，包含 250mg 磷脂酰胆碱、120mg 脱氧胆酸钠、12mg 氯化钠、45mg 苄醇、10mg 乙醇和余量的注射用水)。

[0080] 观察结果表示如下 :(+) :没有包括沉淀、悬浮和相分离在内的现象，并且透明度等于或高于对照的透明度 ;和 (-) :增溶不充分，或者透明度低于对照组的透明度。

[0081] 结果是，如从下表 1 中可见，当添加 PEG 400、尿素、β - 环糊精、山梨醇、司盘 80、泊咯沙姆 188 和甘油时，增溶不充分，而当添加作为添加剂的丙二醇或聚乙二醇 15 羟基硬脂酸酯时，增溶程度与对照相似，且组合物是透明的。因此确定，磷脂酰胆碱、乙醇、苄醇、聚山梨醇酯、丙二醇或聚乙二醇 15 羟基硬脂酸酯以及注射用水的组合可用作无脱氧胆酸钠的含磷脂酰胆碱的可注射组合物。

[0082] 表 1 根据添加剂的溶解性

[0083]

编号	1	2	3	4	5
必需的磷脂材料	250mg	250mg	250mg	250mg	250mg
聚山梨醇酯 80	500mg	500mg	500mg	500mg	500mg
乙醇	500mg	500mg	500mg	500mg	500mg
苄醇	45mg	45mg	45mg	45mg	45mg
其它添加剂	丙二醇 500mg	PEG 400 500mg	尿素 500mg	β-环糊精 100mg	山梨醇 500mg
注射用水	余量	余量	余量	余量	余量
状态	+	-	-	-	-
编号	**6**	**7**	**8**	**9**	
必需的磷脂材料	250mg	250mg	250mg	250mg	
聚山梨醇酯 80	500mg	500mg	500mg	500mg	
乙醇	500mg	500mg	500mg	500mg	
苄醇	45mg	45mg	45mg	45mg	
其它添加剂	斯盘 80 500mg	泊咯沙姆 188 100mg	甘油 500mg	聚乙二醇 15 羟基硬脂酸酯	
注射用水	余量	余量	余量	余量	
状态	-	-	-	+	

[0084] 〈实施例 2〉

[0085] 利用各种浓度的增溶用组合物组分对磷脂酰胆碱的增溶作用进行测试

[0086] 将实施例 1 中选出的组分相互组合以得到各种组分和浓度，并且确定了获得最佳增溶用可注射组合物的条件。

[0087] 按照下表 2 中所示的量将磷脂酰胆碱、聚山梨醇酯 80 和 / 或聚乙二醇 15 羟基硬脂酸酯以及乙醇彼此混合，并且在无光条件下于封闭空间内将混合物在 30℃下以 300rpm 搅拌 30 分钟。

[0088] 在所述混合物中按照下表 2 中所示的量添加丙二醇和 / 或苄醇，并且添加注射用水直至达到 5ml 的总体积。在无光条件下于封闭空间内将所得溶液在 30℃下以 300rpm 搅拌 3 小时，从而制得可注射组合物。

[0089] 进行目视观察以确定以上制备的可注射组合物是否经历包括沉淀、悬浮和相分离在内的现象，以及是否透明。作为对照，使用含脱氧胆酸钠的常规可注射制剂 (5mg 可注射制剂，包含 250mg 磷脂酰胆碱、120mg 脱氧胆酸钠、12mg 氯化钠、45mg 苄醇，10mg 乙醇和余量的注射用水)。

[0090] 观察结果表示如下 :(+) :没有包括沉淀、悬浮和相分离在内的现象，且透明度等于或高于对照的透明度 ;和 (-) :增溶不充分，或者透明度低于对照组的透明度。

[0091] 结果是，如从下表 2 中可见，当未添加丙二醇和苄醇时，增溶效果不充分，而当添加作为添加剂的丙二醇和 / 或苄醇以及聚山梨醇酯和 / 或聚乙二醇 15 羟基硬脂酸酯时，增溶程度充分，与对照相似，并且组合物是透明的。因此确定，磷脂酰胆碱、乙醇、丙二醇和 / 或苄醇以及聚山梨醇酯和 / 或聚乙二醇 15 羟基硬脂酸酯的组合可用作无脱氧胆酸钠的含磷脂酰胆碱的可注射组合物。

[0092] 表 2 根据添加剂浓度的溶解性

[0093]

测试编号	1	2	3	4	5
必需的磷脂材料	287.5mg	287.5mg	287.5mg	287.5mg	287.5mg
丙二醇			500mg	500mg	
苄醇	200mg	100mg			
聚山梨醇酯 80(吐温 80)	120mg	200mg		600mg	600mg
乙醇	1500mg	1500mg	1000mg	500mg	500mg
聚乙二醇 15 羟基硬脂酸酯			500mg	500mg	500mg
注射用水	余量	余量	余量	余量	余量
总计	5ml	5ml	5ml	5ml	5ml
状态	+	+	+	+	-

[0094] 工业实用性

[0095] 从前述内容可见,本发明提供了一种含有磷脂酰胆碱的可注射组合物及其制备方法,所述组合物包含:磷脂酰胆碱;乙醇;丙二醇和/或苄醇;聚山梨醇酯和/或聚乙二醇15羟基硬脂酸酯;以及余量的水或注射用水。本发明的可注射组合物不包含脱氧胆酸钠,并且磷脂酰胆碱在其中得到稳定增溶。因此,本发明提供了更安全的磷脂酰胆碱可注射组合物。

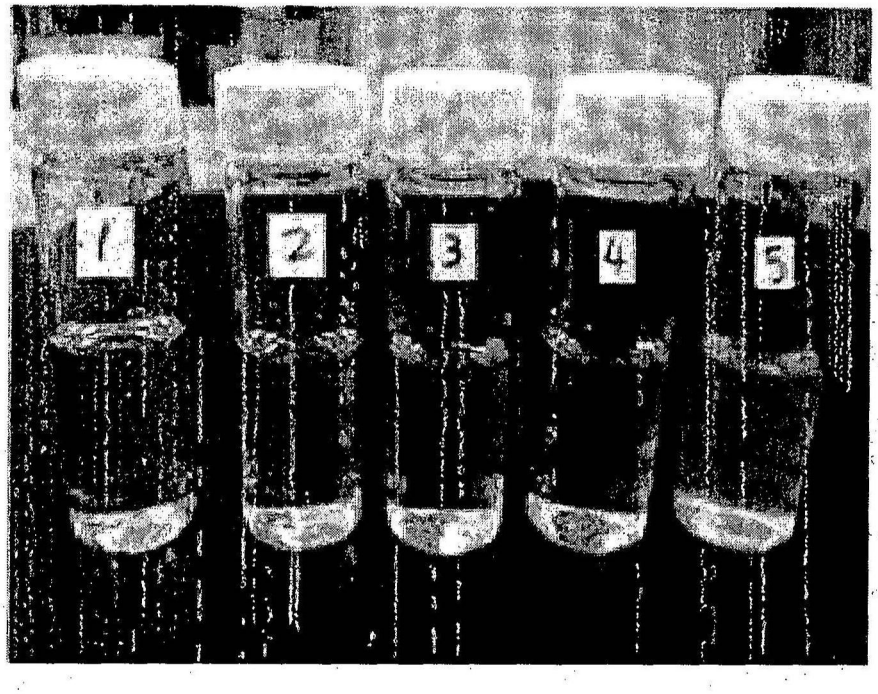

图 1

Abstract

The present invention provides an injectable composition containing phosphatidylcholine comprising phosphatidylcholine; ethanol; propylene glycol and/or benzyl alcohol; polysorbate and/or macrogol 15 hydroxystearate; and a balance of water or water for injection, and a preparing method thereof. An injectable composition of the present invention comprises no sodium deoxycholate which is known as carcinogenic and therefore the more safe injectable composition of phosphatidylcholine can be prepared.