BUTYLPHTHALIDE INTRAVENOUS EMULSION AND APPLICATION THEREOF

FIELD OF INVENTION

The present invention relates to a butylphthalide preparation, and specifically to a butylphthalide intravenous emulsion and application thereof.

BACKGROUND OF THE INVENTION

dl-3-n-Butylphthalide (NBP) also called butylphthalide is dl-3-butylisobenzofuran-1-(3H)-one, which is a racemate. 1-3-n-Butylphthalid is extracted from celery seeds. NBP acts on multiple steps of cerebral ischemia procedure, such as reducing infarct area after focal cerebral ischemia, increasing cerebral blood flow in ischemic area and improving microcirculation in cerebral ischemic area, protecting mitochondrial function, alleviating damage to nerve function, and improving cerebral energy metabolism after total cerebral ischemia. Chinese Patent Nos. 98125618.X, 03137457.3, 200310100222.2 and 200410001748.X respectively disclose the applications of butylphthalide in anti-thrombus and anti-platelet aggregation, the application of 1-n-butylphthalide in prevention and treatment of dementia, cerebral infarction and in manufacture of medicaments for treatment of cerebral ischemia.

Currently butylphthalide preparations available in market are only soft capsules. Since butylphthalide is of an oily liquid form, it can be dissolved in an oil phase or directly processed to form an emulsion, then can be packaged in hard capsules or soft capsules, or can be orally administered directly. However, butylphthalide has a relatively apparent first pass effect which leads to a relatively low bioavailability. In addition, cerebral ischemia patients usually are accompanied with dysphagia or coma, so that capsules cannot meet the clinical requirements for these patients. For cerebral ischemia patients, time is life. Therefore, it is vital to develop a new delivery system suitable for clinical application.

SUMMARY OF THE INVENTION

Since butylphthalide is an oily liquid and hardly dissoluble in water, a specific manufacture technology is employed in the present invention to process butylphthalide into an emulsion for intravenous administration. The butylphthalide intravenous emulsion of the present invention has the following advantages: the drug directly enters into systemic circulation, thus resulting in quick action; the solubility of butylphthalide is improved, resulting in a reduced dosage; and/or the targeting of butylphthalide to brain tissue is improved, thus reducing its toxic side-effects.

The emulsion of the present invention has a particle size of between 10 and 2000 nm, and may be administered via intravenous injection or infusion in order to achieve quick action and brain targeting effect.

The butylphthalide intravenous emulsion of the present invention comprises butylphthalide or derivatives thereof as an active ingredient in an amount of 0.01-50wt%, preferably 0.01-20wt%, more preferably 0.01-10wt%, and an excipient in an amount of 50-99.99wt%, preferably 80-99.99wt%, more preferably 90-99.95%, based on the total weight of the emulsion. The excipient comprises an oil phase, an aqueous phase, an emulsifier, a stabilizer and/or an osmoregulation agent. Butylphthalide or derivatives thereof may be either a racemate of butylphthalide or derivatives thereof, or *l*-butylphthalide or derivatives thereof.

The excipient may comprise an oil phase in an amount of 0-50wt%, preferably 0.1-40wt%, an aqueous phase in an amount of 50-90wt%, preferably 60-97wt%, an emulsifier in an amount of 0.01-50wt%, preferably 0.5-10wt%, a stabilizer in an amount of 0-50wt%, preferably 0-15wt%, and an osmoregulation agent in an amount of 0-10wt%, all based on the total weight of the excipient.

In an aspect of the present invention there is provided a butylphthalide intravenous emulsion comprising butylphthalide or derivatives thereof as an active ingredient in an amount of 0.01-50wt% and an excipient in an amount of 50-99.99wt%, based on the total weight of the emulsion, wherein the excipient comprises an oil phase in an amount of 0.1-40wt% an aqueous phase in an amount of 50-98wt%, an emulsifier in an amount of 0.01-50wt%, a stabilizer in an amount of 0-50wt%, and an osmoregulation agent in an amount of 0-10wt%, based on the total weight of the excipient.

The process for manufacture of the butylphthalide intravenous emulsion of the present invention comprises the steps of, such as preparing emulsion, homogenizing, sterilizing and quality controlling. The step of preparing the primary emulsion is carried out by utilizing ultrasonic method or high-speed shearing method (FA25 Model High Shear Emulsifying Machine, FLUKO Equipment Shanghai Co., Ltd.). The step of homogenizing is

carried out by utilizing a two-stage high pressure emulsifying and homogenizing method (Niro-Soavi NS1001L Model High Pressure Homogenizer and Avestin EmulsiFlex-C5 High Pressure Homogenizer) or microfluidizing technology. The step of sterilizing is carried out by using high pressure sterilizing under rotation. The quality controlling is mainly carried out by measuring particle size.

DETAILED DESCRIPTION OF THE INVENTION

(1) Selection of oil phase

In the emulsion of the present invention, the oil phase generally has an amount in mass of 0~50% (w/v). It is required in the present invention that a therapeutically effective amount of drug should be dissolved in a relatively small amount of oil phase, no drug precipitate occurs or no layer separation occurs under cryogenic storage condition, and in the meantime a stable emulsion is able to be formed with an aqueous phase in the presence of an emulsifier. The oil phase as used in the present invention may be a natural vegetable oil with long chain fatty acid ester groups or a vegetable oil or fatty acid ester being subjected to structure modification and hydrolysis. The examples of those may be one of or a mixture of soybean oil (especially in injection grade), castor oil, tea-seed oil, peanut oil, cottonseed oil, sesame oil, rape oil, safflower oil, olive oil, coconut oil, palm oil and cacao oil; or may be a glyceride with a chain length of C_6~C_{12} fatty acid, such as but not limited to Arlacel 80, Arlacel 86, Capmul MCM, Captex 200 (oil), Captex 355 (oil), Miglyol 812 (oil), Myvacet (oil), Myverol 18-92, glyceride oleate, glyceride linoleate, macrogol glyceryl laurate, ethyl oleate, ethyl linoleate, caprylocaproyl triglyceride, and a mixture thereof; or may be a mixture of the above long chain fatty acid esters and medium-chain fatty acid esters.

During the manufacture of an injection emulsion, a preferred oil phase has relatively little haemolysis effect and is refined. Besides generally used vegetable oils, the following oils may also be used in the present invention:

Arlacel 80 (HLB=4.3)	Sorbitan monooleate
Arlacel 86 (HLB=2.8)	Glyceride oleate: propylene glycol (90:10)

Capmul MCM (HLB=5.5~6.0)	Coconut oil C8/C10 monoglyceride or diglyceride
Captex 200 (oil)	Coconut oil C8/C10 propylene glycol diester
Captex 355 (oil)	Coconut oil C8/C10 triglyceride
Miglyol 812 (oil)	Coconut oil C8/C10 triglyceride
Myvacet (oil)	Purified and acetylated monoglyceride
Myverol 18-92 (HLB-3~7)	Purified sunflower oil monoglyceride (containing 90% of glyceride linoleate)
Peceol (HLB=3)	Glyceride oleate
Maisine (HLB=3)	Glyceride linoleate
Gelucire 44/14 (HLB=14)	Macrogol glyceryl laurate

(2) Selection of emulsifier

The emulsifier as used in the present invention may be one of or a mixture of nonionic surfactants and anionic surfactants.. The preferred emulsifier may be but not limited to one of or a mixture of soybean lecithin or modified soybean lecthin (natural or synthesized), ovolecithin or modified ovolecithin (natural or synthesized), Ophase 31, Poloxamer 108, Poloxamer 188, Poloxamer 407, polyoxyethylene (hydrogenated) castor oil, water soluble VE (TPGS), Solutol HS-15, PEG-400 monostearate, PEG-1750 monostearate, Tween-80, Tween-20, and Span-20. It is preferred to use a mixture of these emulsifiers. During the manufacture of an injection emulsion, the preferred emulsifier has relatively little haemolysis effect and is refined. Besides the above emulsifiers, the following may also be used in the butylphthalide emulsion of the present invention:

Ophase 31 (HLB=4)	Liquid lecithin
Soybean lecithin (HLB=4/7/9)	Soybean lecithin
Cremophor EL (HLB=13.5)	Polyoxyethylene castor oil

Poloxamer 108 (HLB=30.5)	Polyoxyethylene polyoxypropylene ether F-38
Poloxamer 188 (HLB=29)	Polyoxyethylene polyoxypropylene ether F-68
Poloxamer 407 (HLB=21.5)	Polyoxyethylene polyoxypropylene ether F-127
Tween 80 (HLB=15)	Polyoxyethylene sorbitan monoleate
Tween 20 (HLB=16.7)	Polyoxyethylene sorbitan monolaurate
Span 20 (HLB=8.6)	Sorbitan monolaurate

(3) Selection of stabilizer

Suitable stabilizer as used in the present invention may be but not limited to one of or a mixture of oleic acid, sodium oleate, sodium caprylate, cholesterol, cholic acid, deoxycholic acid and sodium salt thereof, vitamin A, vitamin C, and vitamin E.

(4) Selection of osmoregulation agent

Suitable osmoregulation agent as used in the present invention may be but not limited to one of or a mixture of sodium chloride, glucose, sorbitol, xylitol, mannitol, and glycerol.

(5) Basic formulation of butylphthalide intravenous emulsion

In the butylphthalide intravenous emulsion of the present invention, the ratio of butylphthalide : oil phase : emulsifier : aqueous phase : stabilizer : osmoregulation agent is any ratio (by weight) within the range of 0.01~50wt% : 0~50wt% : 0.01~50wt% : 50~98wt% : 0~50wt% : 0~10wt%.

In one embodiment, the butylphthalide intravenous emulsion of the present invention has the following composition:

Butylphthalide	10g
Oil phase	100g
Emulsifier	50g
Stabilizer	50g

Aqueous phase	Added to 1000ml

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	10
Soybean lecithin	12
Soybean oil	100
Vitamin E	1
Sorbitol	25
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, vitamin E and soybean oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Soybean lecithin and sorbitol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 2: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	15
Castor oil	100

Soybean lecithin	12
Poloxamer 188	6
Glycerol	25
Oleic acid	10
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, soybean lecithin, oleic acid and castor oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 3: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	20
Soybean lecithin	12
Olive oil	100
Cholic acid	1
Mannitol	20
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, cholic acid and olive oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C

water bath. Soybean lecithin and mannitol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was treated with ultrasonic waves for 10 times (10 seconds for each time, power: 400W). Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 4: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	25
Cottonseed oil	100
Ovolecithin	12
Poloxamer 188	20
Glycerol	25
Sodium oleate	10
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, ovolecithin, sodium oleate and cottonseed oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for

protection during the whole process.

Example 5: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	30
Soybean lecithin	12
Soybean oil	200
Tween 80	6
Vitamin E	8
Xylitol	100
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, Tween 80, vitamin E and soybean oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Soybean lecithin and xylitol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 6: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	40
Caprylocaproyl triglyceride	200

Soybean lecithin	12
Poloxamer 188	20
Glycerol	25
Oleic acid	10
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, soybean lecithin, oleic acid and caprylocaproyl triglyceride were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 7: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	50
Soybean lecithin	15
Sesame oil	100
Vitamin E	8
Glycerol	22.5
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, vitamin E and sesame oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C

water bath. Soybean lecithin and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 8: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	20
Soybean oil	100
Ovolecithin	12
Poloxamer 188	20
Glycerol	25
Sodium oleate	10
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, ovolecithin, sodium oleate and soybean oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for

protection during the whole process.

Example 9: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	100
Ovolecithin	20
Poloxamer 188	20
Glycerol	25
Sodium oleate	30
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, ovolecithin and sodium oleate were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 10: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	0.1
Soybean oil	100
Ovolecithin	19

Poloxamer 188	25
Glycerol	25
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, ovolecithin and soybean oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 and glycerol were weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

Example 11: Preparation of butylphthalide intravenous emulsion

Formula composition	(g)
Butylphthalide	5
Soybean oil	100
Ovolecithin	12
Poloxamer 188	20
Sodium oleate	3
Water for injection	Added to 1000ml

The preparation process comprises the steps of: butylphthalide, ovolecithin, sodium oleate and soybean oil were weighed and mixed to form an oil phase, and the oil phase was pre-heated in a 60°C water bath. Poloxamer 188 was weighed and dispersed in water to form an aqueous phase, and the aqueous phase was pre-heated in a 60°C water bath. The oil phase

was slowly poured into the aqueous phase, and the mixture was dispersed by using a high shear emulsifying machine under 10,000 rpm for 5 min. Then the mixture was circulated in a high pressure homogenizer for 5 times, in which the first stage pressure is 100MPa and the second stage pressure is 10MPa. Then the emulsion was regulated to have a pH of 8, filtered, subpackaged and sterilized at 121°C for 15min. Nitrogen gas is fed for protection during the whole process.

CLAIMS

1. A butylphthalide intravenous emulsion comprising butylphthalide or derivatives thereof as an active ingredient in an amount of 0.01-50wt% and an excipient in an amount of 50-99.99wt%, based on the total weight of the emulsion, wherein the excipient comprises an oil phase in an amount of 0.1-40wt%, an aqueous phase in an amount of 50-98wt%, an emulsifier in an amount of 0.01-50wt%, a stabilizer in an amount of 0-50wt%, and an osmoregulation agent in an amount of 0-10wt%, based on the total weight of the excipient.

2. The butylphthalide intravenous emulsion according to claim 1, wherein the butylphthalide or derivatives thereof is a racemate of butylphthalide or derivatives thereof, or *l*-butylphthalide or derivatives thereof.

3. The butylphthalide intravenous emulsion according to claim 1, wherein the oil phase comprises a natural vegetable oil with long chain fatty acid ester groups, or a vegetable oil or fatty acid ester being subjected to structure modifications and hydrolysis, or glyceride with a chain length of C_6-C_{12} fatty acid, or a mixture thereof.

4. The butylphthalide intravenous emulsion according to claim 3, wherein the oil phase is one of or a mixture of soybean oil, castor oil, tea-seed oil, peanut oil, cottonseed oil, sesame oil, rape oil, safflower oil, olive oil, coconut oil, palm oil, cacao oil, Arlacel 80, Arlacel 86, Capmul MCM, Captex 200 (oil), Captex 355 (oil), Miglyol 812 (oil), Myvacet (oil), Myverol 18-92, glyceride oleate, glyceride linoleate, macrogol glyceryl laurate, ethyl oleate, ethyl linoleate, and caprylocaproyl triglyceride.

5. The butylphthalide intravenous emulsion according to claim 1, wherein the emulsifier comprises one of or a mixture of nonionic surfactants and anionic surfactants.

6. The butylphthalide intravenous emulsion according to claim 5, wherein the emulsifier is one of or a mixture of soybean lecithin or modified soybean lecthin, ovolecithin or modified ovolecithin, Ophase 31, Poloxamer 108, Poloxamer 188, Poloxamer 407, polyoxyethylene (hydrogenated) castor oil, water soluble VE (TPGS), Solutol HS-15, PEG-400 monostearate, PEG-1750 monostearate, Tween-80, Tween-20, and Span-20.

7. The butylphthalide intravenous emulsion according to claim 1, wherein the stabilizer is one of or a mixture of oleic acid, sodium oleate, sodium caprylate, cholesterol, cholic acid, deoxycholic acid and sodium salt thereof, vitamin A, vitamin C, and vitamin E.

8. The butylphthalide intravenous emulsion according to claim 1, wherein the osmoregulation agent is one of or a mixture of sodium chloride, glucose, sorbitol, xylitol, mannitol, and glycerol.

9. The butylphthalide intravenous emulsion according to claim 1, which is administered by intravenous injection or infusion.

10. A butylphthalide intravenous emulsion according to claim 1 and substantially as herein described with reference to any one of Examples 1 to 11.

11. The butylphthalide intravenous emulsion according to any one of claims 1 to 8 or 10, wherein the emulsion has a particle size of between 10 and 200 nm.