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(54) Invention title

A type of aprepitant microemulsion for injection and its preparation method

(57) Abstract

The invention discloses an aprepitant microemulsion for injection, which is composed of the following mass percentage components: 0.05% 2% BAJ aprepitant, 5% ~ 30% injection oil, 0.5% ~ 10% emulsifier , 1~10% emulsifier, 5%~20% protective agent: 60~80% water for injection. Compared with existing aprepitant oral dosage forms, the outstanding advantages of the aprepitant microemulsion for injection of the present invention include:Since aprepitant is insoluble in water and insoluble in organic solvents, in order to achieve aprepitant injection, the present invention successfully prepares aprepitant microemulsion and aprepitant microemulsion freeze-dried powder, which can achieved large-scale industrial production. Compared with fosaprepitant dimeglumine injection, the cost is greatly reduced, has good practicability, and can produce better economic and social benefits.

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1. A type of aprepitant microemulsion for injection, characterized in that: Composed of the following mass percentage components: 0.05% ~ 2% aprepitant, 5% ~ 30% injection oil, 0.5% ~ 10% emulsifier, 1 ~ 10% co-emulsifier, 5% ~ 20% protection agent; 60~80% water for injection; the oil for injection is one or more of soybean oil for injection, ethyl oleate, polyethylene glycol glyceryl oleate, triglycerides with medium fatty chain length, isopropyl myristate, peanut oil, corn oil, and olive oil; the emulsifier is one or more of phospholipids, poloxamer, polyoxyethylene castor oil and derivatives, polyethylene glycol-caprylic/capric glyceryl, and polysorbate 80; the co-emulsifier is one or more of ethanol, glycerol, 1,2-propanediol, and polyethylene glycol 400; the protective agent is one or more of glycerol, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids.

2. An aprepitant microemulsion for injection according to claim 1, characterized in that: Specifications are 1 ~ 1000ml/dose.

3. Aprepitant microemulsion for injection according to claim 1, characterized in that:The dosage forms are small injections, infusions and freeze-dried powder injections suitable for clinical intravenous administration.

4. According to the claims; the aprepitant microemulsion for injection is characterized in that:The specifications of freeze-dried powder are 10 ~ 100mg/tube.

5. Aprepitant microemulsion for injection according to claim 1, characterized in that:The injection oil is soybean oil for injection.

6. Aprepitant microemulsion for injection according to claim 1, characterized in that:The emulsifier is egg yolk phospholipid.

7. Aprepitant microemulsion for injection according to claim 1, characterized in that:The emulsifier is ethanol.

8. Aprepitant microemulsion for injection according to claim 1, characterized in that:The protective agent used is glycerol.

9. Aprepitant microemulsion for injection according to claim 1, characterized in that:Composed of the following mass percentage components: 1.0% ~ 1.5% aprepitant, 7% ~ 15% injection oil, 8% ~ 10% emulsifier, 2 ~ 5% co-emulsifier, 8% ~ 13% protection agent; water for injection 60~69%.

10. A method for preparing the aprepitant microemulsion for injection according to claim 1, characterized in that it comprises the following steps:

Mix aprepitant and emulsifier, dissolve with ethanol, heat and stir at 60°C until the ethanol evaporates to a viscous state, continue to control the temperature at 60°C, heat and dissolve, and prepare the crude emulsifier; add co-emulsifier to the coarse emulsifier, add an appropriate amount of ethanol to dissolve, control the temperature to 60°C, and stir until a clear oil phase is obtained; dissolve the protective agent with water for injection heated to 60°C to obtain the water phase; mix the clear oil phase and the water phase, stir at high speed, mash, and add an appropriate amount of water for injection at the same time to adjust the pH to 6.0~8.0 to obtain initial solution; add the initial solution into a high-pressure homogenizer and use the homogenization method, control the pressure around 1000MPa, and homogenize multiple times to prepare aprepitant microemulsifier for injection; fill and autoclave.

A type of aprepitant microemulsion for injection and preparation method

Technical field

[0001] The invention belongs to the technical field of pharmaceutical preparations, and specifically relates to an injectable aprepitant microemulsion and a preparation method thereof.

Background technique

[0002] Aprepitant (aprepitanl) is an NK-1 receptor antagonist currently marketed for antiemetic use. The NK-1 receptor is the binding site for tachykinin (NKA) substance P (SP) and is located in the brainstem vomiting center and gastrointestinal tract. Animal experiments have proven that SP can induce vomiting. Drugs that specifically block this receptor can prevent vomiting caused by all emetic stimuli, including cisplatin. Aprepitant is an NK-1 receptor blocker that blocks the effects of substance P by binding to NK-1 receptors (mainly found in the central nervous system and its periphery). Aprepitant can pass through the blood-brain barrier and occupy the NK-1 receptor in the brain, with selectivity and high affinity, but has very low affinity for NK-2 and NK-3 receptors. Aprepitant is the only NK-1 receptor drug currently on the market. Its complete antiemetic control rate is 14.98% higher than that of 5-hydroxytryptamine receptor antagonist drugs.

[0003] Multiple clinical studies have proven that antiemetic regimens containing aprepitant are more effective in preventing acute and delayed CINV caused by drugs with high and medium emetogenic risks (especially cisplatin-based chemotherapy drugs), and does not aggravate adverse reactions. Aprepitant is also a moderate inhibitor of cytochrome P450 (CYP) 3A4. Theoretically, because some antiemetics (such as glucocorticoids) and chemotherapy drugs (such as cyclophosphamide and docetaxel) are substrates of CYP3A4, their metabolism will be affected when they are combined with aprepitant. Therefore, the dose of corticosteroids should be reduced when co-administered with aprepitant. However, this does not apply to those receiving glucocorticoid-containing chemotherapy regimens. At present, there is no clinical evidence that the combination of aprepitant with standard usage and dosage and the above mentioned chemotherapy drugs will cause clinical sequelae. The new guidelines recommend that aprepitant should only be used according to the established dosage and schedule.

[0004] Tumor is a disease that seriously threatens human life and quality of life. Currently, there are more than 10 million patients worldwide receiving radiotherapy and chemotherapy. However, side effects related to tumor treatment are serious and frequent; cancer patients and individuals whose disease has reached a progressive stage often suffer from pain and bone complications (malignant tumor-related hypercalcemia and bone metastasis, etc.), nausea and vomiting, etc. The above mentioned side effects and complications must be treated promptly to ensure that cancer patients can continue to receive treatment and have a better quality of life. Cancer treatment support therapy was developed for this purpose. It has attracted great attention from many of the world's leading pharmaceutical companies and biotechnology companies. After about fifteen years of cultivation, it has formed a huge market field that is still growing rapidly today. Nausea and vomiting are another of the most common side effects associated with cancer chemotherapy, affecting about 85% of patients.

[0005] Microemulsion is a new type of pharmaceutical preparation. It is a transparent or translucent, low-viscosity, isotropic thermodynamically stable solution system formed spontaneously from water phase, oil phase, surfactant and co-surfactant in appropriate proportions. The system has uniform particle size. Microemulsion preparations can improve the solubility of poorly water-soluble drugs and fat-soluble drugs, promote the absorption of macromolecular drugs in the body, and improve bioavailability. To a certain extent, it can protect drugs from enzymatic degradation in the gastrointestinal tract and enhance the stability of unstable drugs. The particle size is small and uniform, which improves the dispersion of contained drugs and promotes transdermal absorption of drugs. Since the particle size of microemulsion droplets is smaller than that of red blood cells and the viscosity is low, it can be directly injected and is often used for the injection of poorly soluble drugs. Therefore,

microemulsions are increasingly favored by medical workers as drug carriers, especially in injection drug delivery.

[0006] Aprepitant capsules are currently used for vomiting caused by radiotherapy and chemotherapy in clinical cancer patients. For patients with severe vomiting, oral administration brings great inconvenience to the patient, and the absorption and bioavailability of the drug are also greatly reduced. The injection form of aprepitant is of great significance for clinical treatment. Although the prodrug of aprepitant, fosaprepitant dimeglumine injection, is currently available, it is actually synthesized through complex reactions on the basis of aprepitant, which increases the cost and greatly increases the burden on patients.

Summary of the invention

[0007] Purpose of the invention:In view of the deficiencies in the prior art, the purpose of the present invention is to provide an injectable aprepitant microemulsion to effectively solve the problems of inconvenient clinical application of oral aprepitant, poor absorption, and low bioavailability. Another object of the present invention is to provide a method for preparing the above mentioned aprepitant microemulsion for injection. Another object of the present invention is to provide a method for preparing the above mentioned injectable aprepitant microemulsion small water injection, infusion solution and freeze-dried powder injection.

[0008] Technical solutions:In order to achieve the above mentioned object of the invention, the technical solutions adopted by the present invention are as follows:

A type of aprepitant microemulsion for injection, characterized in that:Composed of the following mass percentage components: 0.05% ~ 2% aprepitant, 5% ~ 30% injection oil, 0.5% ~ 10% emulsifier, 1 ~ 10% co-emulsifier, 5% ~ 20% protection agent; water for injection 60 ~ 80%.

[0009] The preferred mass percentage of each component is: 1.0% ~ 1.5% aprepitant, 7% ~ 15% injection oil, 8% ~ 10% emulsifier, 7 ~ 13% co-emulsifier, 8% ~ 13% protection agent; water for injection 60 ~ 69%.

[0010] The injection oil used is one or more of soybean oil for injection, ethyl oleate, oleic acid polyethylene glycol glyceride, triglycerides of medium fatty chain length, isopropyl myristate, peanut oil, corn oil, olive oil, with soybean oil being preferred. The emulsifier used is one or more of phospholipids, poloxamer, polyoxyethylene castor oil and derivatives, polyethylene glycol-caprylic/capric glyceride, and polysorbate 80, with egg yolk phospholipids being preferred. The co-emulsifier used is one or more of ethanol, glycerin, 1,2-propanediol, and polyethylene glycol 400, with ethanol being preferred. The protective agent used is one or more of glycerin, sucrose, trehalose, glucose, xylitol, mannitol, and amino acids, with glycerin being preferred.

[0011] The pH value of the aprepitant microemulsion for injection is 6.0 ~ 8.0.

[0012] The particle size of the aprepitant microemulsion for injection is 50nm~150nm.

[0013] The particle size of the aprepitant microemulsion small injection and freeze-dried powder for injection is below 200 nm after dilution with an isotonic physiologically compatible solution.

[0014] Aprepitant microemulsion for injection, specifications are 1 ~ 1000ml/dose.

[0015] The dosage forms are small injections, infusions and freeze-dried powder injections suitable for clinical intravenous administration. The specifications of freeze-dried powder are 10 ~ 100mg/tube.

[0016] A method for preparing aprepitant microemulsion for injection, comprising the following steps:

Mix aprepitant and emulsifier, dissolve with ethanol, heat and stir at 60°C until the ethanol evaporates to a viscous state, continue to control the temperature at 60°C, heat and dissolve, and prepare the crude emulsifier; add co-emulsifier to the coarse emulsifier, add an appropriate amount of ethanol to dissolve, control the temperature to 60°C, and stir until a clear oil phase is obtained; dissolve the protective agent with water for injection heated to 60°C to obtain the water phase; mix the clear oil phase and the water phase, stir at high speed, mash, and add an appropriate amount of water for injection at the

same time to adjust the pH to 6.0~8.0 to obtain initial solution; add the initial solution into a high-pressure homogenizer and use the homogenization method, control the pressure around 1000MPa, and homogenize multiple times to prepare aprepitant microemulsifier for injection; fill and autoclave.

[0017] Beneficial effects: Compared with existing aprepitant oral dosage forms, the injectable aprepitant microemulsion of the present invention has outstanding advantages including:Since aprepitant is insoluble in water and insoluble in organic solvents, in order to achieve aprepitant injection, the present invention successfully prepares aprepitant microemulsion and aprepitant microemulsion freeze-dried powder, which can achieve large-scale industrial production. Compared with fosaprepitant dimeglumine injection, the cost is greatly reduced, has good practicability, and can produce better economic and social benefits.

Detailed description

[0018] The present invention will be further described below in conjunction with specific embodiments.

[0019] Embodiment 1

Aprepitant microemulsion for injection consists of various components: 0.5g aprepitant, 30g soybean oil, 3g egg yolk phospholipid, 1.5g ethanol, 5g glycerin, 60g water for injection.

[0020] Preparation: Mix aprepitant and egg yolk phospholipid, dissolve with ethanol, heat and stir at 60°C until the ethanol evaporates to a viscous state, continue to heat and dissolve, stir until uniform, and control the temperature at 60°C to prepare the crude emulsifier; add soybean oil to the crude emulsifier, add an appropriate amount of ethanol to dissolve; continue to heat and stir at 60°C until a clear oil phase is obtained; dissolve glycerin in water for injection heated to 60°C to obtain water phase; mix the clarified oil phase and the water phase, stir at high speed, mash, and add an appropriate amount of water for injection to adjust the pH to 7.2 to obtain initial solution; add the emulsifier into a high-pressure homogenizer using the homogenization method, control the pressure at about 1000MPa, homogenize three times, and filter and sterilize with a 0.22 μm membrane to prepare aprepitant microemulsion for injection.

[0021] Embodiment 2

Aprepitant microemulsion for injection consists of various components: 2g aprepitant, 5g ethyl oleate, 10g poloxamer, 3g glycerol, 20g sucrose, 60g water for injection.

[0022] Mix aprepitant and poloxamer, dissolve with an appropriate amount of ethanol, heat and stir at 60°C until the ethanol evaporates and becomes viscous, continue to heat and dissolve, stir until uniform, and control the temperature at 60°C to prepare the crude emulsifier; add ethyl oleate to the crude emulsifier and add an appropriate amount of ethanol to dissolve; continue heating and stirring at 60°C until a clear oil phase is obtained; dissolve sucrose with water for injection heated to 60°C to obtain a water phase, mix the clear oil and water phase, stir at high speed, mash, and add an appropriate amount of water for injection at the same time to adjust the pH to 6.8 to initial solution; add the initial solution into a high-pressure homogenizer using the homogenization method, control the pressure at about 1000MPa, homogenize three times, and filter and sterilize with a 0.22 μm membrane to prepare aprepitant microemulsion for injection.

[0023] Embodiment 3

Aprepitant microemulsion for injection consists of various components: 0.05g aprepitant, 6g peanut oil, 6g polysorbate 80, 2g polyethylene glycol 400, 5.95g glucose, 80g water for injection.

[0024] The preparation method is the same as in Embodiment 2, except that the pH of colostrum is 8.0.

[0025] Embodiment 4

Aprepitant microemulsion freeze-dried powder for injection consists of various components: 0.5g aprepitant, 15g soybean oil, 6.5g egg yolk phospholipid, 1g ethanol, 8g glycerin, 69% water for injection.

[0026] The preparation method of the emulsion is the same as in Embodiment 2. The prepared aprepitant microemulsion for injection is pre-lyophilized at -55°C for 12 hours and vacuum freeze-dried for 80 hours. Aprepitant microemulsion freeze-dried powder for injection was prepared.

[0027] Embodiment 5:

Aprepitant microemulsion small injection for injection consists of various components: 2g aprepitant, 20g soybean oil, 10g egg yolk phospholipid, 3g ethanol, 5g glycerin, 60g water for injection.

[0028] Mix aprepitant in egg yolk phospholipid, dissolve it in ethanol, heat and stir at 60°C until the ethanol evaporates and becomes viscous; continue to dissolve by heating, stir until uniform, and control the temperature at 60°C to prepare the crude emulsifier; add soybean oil to the crude emulsifier and add an appropriate amount of ethanol to dissolve; continue heating and stirring at 60°C until a clear oil phase is obtained; dissolve glycerin in water for injection heated to 60°C to obtain a water phase; mix the clear oil phase and water phase, stir at high speed, mash, and add an appropriate amount of water for injection at the same time to adjust the pH to 6.8 to obtain the initial solution; add the initial solution into a high-pressure homogenizer using the homogenization method, control the pressure at about 1000MPa, and homogenize three times to prepare aprepitant microemulsion for injection. Sterilize by filtration through a 0.22 μm membrane. (6) After passing the inspection, fill the microemulsion containing 115 mg of aprepitant into a 5 ml glass bottle with nitrogen, sterilize it by autoclaving at 115°C for 30 minutes, and quickly cool it down in an ice-water bath to prepare a small injection of aprepitant.

[0029] Embodiment 6

Aprepitant microemulsion small injection for injection consists of various components: 0.5g aprepitant, 15g soybean oil, 0.5g egg yolk phospholipid, 10g ethanol, 5g glycerol, 69g water for injection.

[0030] The preparation method is the same as Embodiment 5, wherein the pH of the aprepitant microemulsion is 7.2, and the 5 ml glass bottle contains 150 mg of aprepitant.

[0031] Embodiment 7:Preparation of aprepitant microemulsion infusion.

[0032] Aprepitant microemulsion infusion for injection consists of various components: 0.2g aprepitant, 9.5g soybean oil, 9.8g egg yolk phospholipid, 5.5g ethanol, 1g glycerin, 74g water for injection.

[0033] Mix aprepitant and egg yolk phospholipid, dissolve in ethanol, heat and stir at 60°C until the ethanol evaporates and becomes viscous; heat to dissolve, stir until uniform, and control the temperature at 60°C to prepare the crude emulsifier; add soybean oil to the crude emulsifier and add an appropriate amount of ethanol to dissolve; continue heating and stirring at 60°C until a clear oil phase is obtained; dissolve glycerin in water for injection heated to 60°C to obtain the water phase; mix the clarified oil phase and the water phase, stir at high speed, mash, and add an appropriate amount of water for injection to adjust the pH to 8.0 to obtain the initial solution; add the initial solution into a high-pressure homogenizer and use the homogenization method, control the pressure to about 1000MPa, and homogenize three times to prepare aprepitant microemulsion for injection. Sterilize by filtration through a 0.22 μm membrane. After passing the clarification inspection, add the microemulsion containing 115mg of aprepitant to the injection solution, fill it with nitrogen into a 100ml glass bottle with physiological saline, and sterilize it by hot-pressing at 115°C for 30 minutes to prepare the aprepitant microemulsion infusion.

[0034] Embodiment 8:Preparation of aprepitant microemulsion infusion.

[0035] Aprepitant microemulsion infusion for injection is composed of each component: 1.0g aprepitant, 10g olive oil, 10g polyethylene glycol-caprylinyl glyceride, 10g 1,2-propanediol, 8g xylitol, 61g water for injection.

[0036] The preparation method is the same as Embodiment 7, wherein the pH of aprepitant microemulsion is 7.2, and the 250ml glass bottle contains 150 mg of aprepitant.

TRANSPERFECT

City of New York, State of New York, County of New York

The attached was translated by Karen Lee, a professional translator who is fluent in Mandarin Chinese and English and have personal knowledge of the facts stated herein.

Attached hereto is a document entitled ("CN102379845A_OriginalPublication_EN") which is a true and accurate translation of ("CN102379845A_OriginalPublication") from Chinese to English.

Shayna Himelfarb

Sworn to before me this
November 28, 2023

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