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(54) Title: PROCESS FOR THE PREPARATION OF HOMOGENEOUS SUSPENSIONS FOR THE INHALATION BY NEBULIZATION

(57) Abstract: The invention relates to a simple, rapid, cost effective, time-saving and industrially convenient process for the preparation of suspensions to be used in pharmaceutical formulations comprising ivermectin as an active agent for inhalation by nebulization. Further, the present invention also relates to inhalation compositions comprising ivermectin, isotonic agents, buffering agents, dispersing or suspending agents.

Description

PROCESS FOR THE PREPARATION OF HOMOGENEOUS SUSPENSIONS FOR THE INHALATION BY NEBULIZATION

Field of Invention

The invention relates to a simple, rapid, cost effective, time-saving and industrially convenient process for the preparation of suspensions to be used in pharmaceutical formulations comprising ivermectin as an active agent for inhalation by nebulization. Further, the present invention also relates to inhalation compositions comprising ivermectin, isotonic agents, buffering agents, dispersing or suspending agents.

The background of the invention

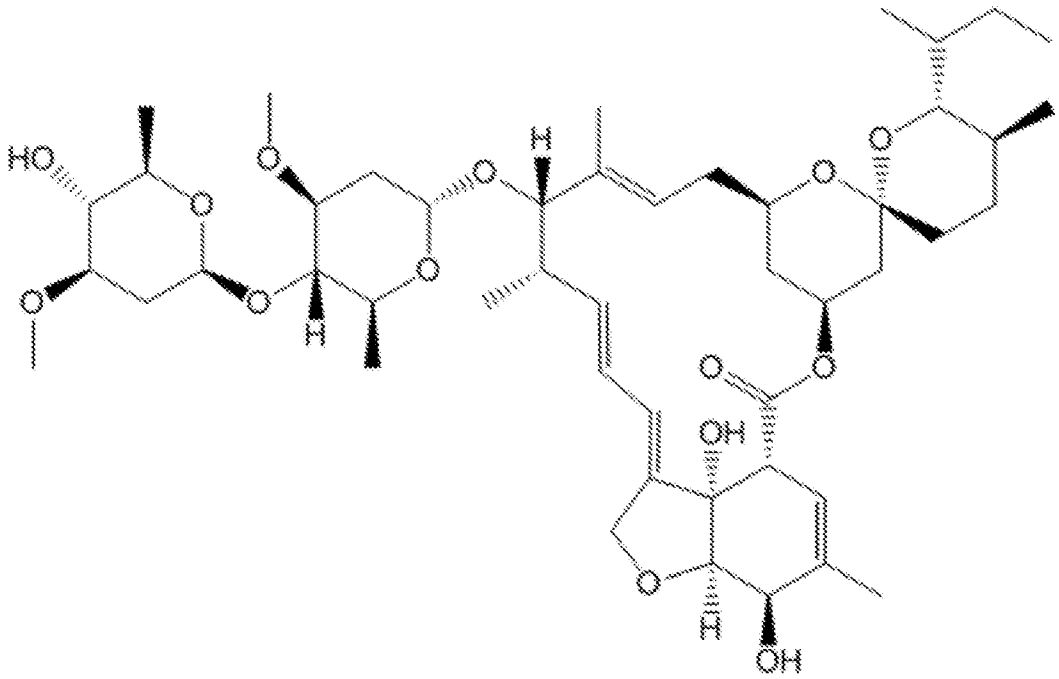
Ivermectin is a semisynthetic, anthelmintic agent derived from the avermectins, a class of highly active broad-spectrum anti-parasitic agents isolated from Streptomyces avermitilis with antiparasitic activities. Upon administration, ivermectin exerts its anthelmintic effect through binding and activating glutamate-gated chloride channels (GluCls) expressed on nematode neurons and pharyngeal muscle cells. This causes increased permeability of chloride ions, causing a state of hyperpolarization and results in the paralysis and death of the parasite. Because of this, Ivermectin is an anti-helminthic drug that is used for the treatment of many parasitic infections which include head lice, scabies, river blindness (onchocerciasis), strongyloidiasis, lymphatic filariasis, trichuriasis, and ascariasis.

Ivermectin was discovered in 1975 and came into medical use in 1981. Ivermectin is a Food and Drug Administration (FDA)-approved as an antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies. It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock. For these indications, ivermectin has been widely used and is generally well tolerated.

Ivermectin is also used to treat infection with parasitic arthropods. Scabies – infestation with the mite Sarcoptes scabies – is most commonly treated with topical permethrin or oral ivermectin. For most scabies cases, ivermectin is used in a two-dose regimen: a first dose kills the active mites, but not their eggs. Over the next week, the eggs hatch, and a second dose kills the newly hatched mites. For severe "crusted scabies", the Centers for Disease Control

recommends up to seven doses of ivermectin over the course of a month, along with a topical antiparasitic. Both head lice and pubic lice can be treated with oral ivermectin, a 0.5% ivermectin lotion applied directly to the affected area or various other insecticides. Ivermectin is also used to treat rosacea and blepharitis, both of which can be caused or exacerbated by Demodex folliculorum mites. In addition these, ivermectin has been described in the literature to have antiviral effects. Ivermectin has antiviral effects against several distinct positive-sense single-strand RNA viruses.

Ivermectin is an approximately 80:20 mixture of two avermectin B1 derivatives, called 22,23-dihydroavermectin B1a and B1b. Its chemical name is (1R,4S,5'S,6R,6'R,8R,10E,12S,13S,14E,16E,20R,21R,24S)-6'-[(2S)-butan-2-yl]-21,24-dihydroxy-12-[(2R,4S,5S,6S)-5-[(2S,4S,5S,6S)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]oxy-4-methoxy-6-methyloxan-2-yl]oxy-5',11,13,22-tetramethylspiro[3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene-6,2'-oxane]-2-one and its chemical structure is shown in Formula I.



Formula I

As mentioned above, ivermectin is an agent used in a wide spectrum of use in animals and humans. Ivermectin can be given by mouth, topically, or via injection. It does not readily cross the blood–brain barrier of mammals due to the presence of P-glycoprotein (the MDR1 gene mutation affects function of this protein).

Taking a lower dose of ivermectin by inhalation from the lungs instead of taking a high dose orally is beneficial for patient compliance.

Among the inhalation techniques, nebul products are easier to use. Nebulizers have a relatively simple usage technique compared to Metered Dose Inhaler and Dry Powder Inhaler devices. A metered-dose inhaler requires hand-breath coordination and an adequate flow rate for a Dry Powder Inhaler. Nebulizer devices can be selected for patients who cannot use these two devices effectively. The medicine produced in the form of nebules from these devices can be delivered to the lungs by inhaling and exhaling with a mouthpiece or mask.

Efficient access of the inhaler formulations to the lungs is achieved by optimizing the formulation and process steps with the device, active and auxiliary components. In order to ensure effective delivery of ivermectin to the lungs, the excipients included in the drug formulation must be properly selected, quantified, and included in the process in determining steps.

The dispersing or suspending agents used in a certain order in the process steps and their weight ratio are important in terms of increased stability, enhanced fine particle dose, fine particle fraction, delivery rate, and total active agent values. Also, the type of dispersing agents has a critical effect on these quality parameters and accordingly on the performance of the suspension product.

The steps of adding dispersing or suspending agents used in the process to the process and their weight ratios of applied are of great importance in order to ensure homogenization and prevent losses in the process.

Considering the state of art, there is still a need for innovative processes that will solve the homogenization problem, and which will provide a standardized method for the fast, robust and reproducible production of stable homogeneous suspension inhalation compositions with enhanced FPF, delivery rate and total active ingredient values.

Objects and Brief Description of the Invention

The main object of the present invention is to provide a production method for preparing pharmaceutical ivermectin compositions for inhalation which eliminates all aforesaid problems and brings additional advantages to the relevant prior art.

Another object of the present invention is to provide a process for the preparation of suspensions to be used in pharmaceutical formulations for inhalation by nebulization for use in the prevention, treatment, or the alleviation of the symptoms of respiratory diseases.

Another object of the present invention is to provide a process for the preparation of suspensions to be used in pharmaceutical formulations for inhalation by nebulization with increased stability, enhanced fine particle dose (FPD), fine particle fraction (FPF), delivery rate and total active agent values.

Another object of the present invention is to provide a process for the preparation of suspensions to be used in pharmaceutical formulations for inhalation by nebulization with enhanced uniformity and homogeneity.

Another object of the present invention is to obtain suspensions provided by the above-mentioned process comprising ivermectin.

A further object of the present invention is to obtain suspensions comprising ivermectin.

Another object of the present invention is to obtain inhalation compositions comprising ivermectin or a pharmaceutically acceptable salt thereof.

Another object of the present invention is to obtain suspension compositions comprising ivermectin, isotonic agents, buffering agents, dispersing or suspending agents.

Another object of the present invention is to describe a process for forming suspension formulations to be delivered to the patient via nebulization.

Another object of the present invention is to access of inhaler formulations to the lungs is achieved.

Detailed description of the invention

In accordance with the objects outlined above, detailed features of the present invention are given herein.

The present invention relates to a process for the preparation of homogeneous suspensions to be used in pharmaceutical formulations for inhalation by nebulization, which comprises the following steps:

a- obtaining Mixture 1 by:
(i) heating the water for injection
(ii) adding respectively the first dispersing or suspending agent, the second dispersing or suspending agent and mixing
(iii) adding ivermectin and mixing
b- obtaining Mixture 2 by:
(i) heating the water for injection
(ii) adding respectively isotonic agent, and at least two buffering agents, and mixing
c- mixing the Mixture 1 and Mixture 2

wherein the temperature of water for injection is 45°C-55°C and the weight ratio of first dispersing or suspending agent to second dispersing or suspending agent is between 15:1-5:1, preferably 12:1-5:1, more preferably 10:1-5:1.

The heating is performed in the step numbered a) (i) and b) (i). The reason for heating is to increase the solubility/distribution of the excipients to be added. According to one embodiment, the temperature of the water for injection is 45°C-55°C.

Another important factor is the preparation of a suitable dispersing medium by including the dispersing or suspending agents in the process before the active agents to help disperse the active agents that is insoluble in water.

The main purpose of dispersing a powder in a liquid is to separate primary particles from aggregates and agglomerates and then stabilize them in the liquid medium. This requires an effective dispersing or suspending agent that adsorbs very quickly at the solid/liquid interface. The main criterion for an effective dispersing or suspending agent is strong adsorption or attachment to the particle surface. This requires the dispersing or suspending agent to be attached to the active agent particle surface at multiple points.

In addition, another role of the dispersing or suspending agent in suspension is to reduce the surface energy of the powder. This facilitates the decomposition and homogeneous dispersion stages of the agglomerates of the particles in the subsequent homogenization.

Although the first dispersing or suspending agent alone could not provide the medium to suspend the active agent, the desired quality profile was achieved when the second dispersing or suspending agent was added. Likewise, although the second dispersing or suspending agent alone could not provide the medium to suspend the active agent, the desired quality profile was achieved when the first dispersing or suspending agent was added. The inventors have surprisingly been found that when the first dispersing or suspending agent and the second dispersing or suspending agent are added to the mixture together, a homogeneous final product can be obtained. One of the most important factors that lead to the desired quality profile is the weight ratio of the first dispersing or suspending agent to the second dispersing or suspending agent.

According to the one embodiment, the first dispersing or suspending agent is selected from the group comprising polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), polysorbate 80 (polyoxyethylene (20) sorbitan monooleate), sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate (SpanR85), sorbitan mono-oleate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate or mixtures thereof.

According to the preferred embodiment, the first dispersing or suspending agent is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

According to the one embodiment, the second dispersing or suspending agent is selected from the group comprising polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), sorbitan monolaurate (span 20), sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate (SpanR85), sorbitan mono-oleate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate or mixtures thereof.

According to the preferred embodiment, the second dispersing or suspending agent is sorbitan monolaurate (span20).

According to preferred embodiment, the weight ratio of first dispersing or suspending agent to second dispersing or suspending agent is 15:1- 5:1, preferably 12:1-5:1, more preferably 10:1-5:1.

According to the preferred embodiment, the active agent is selected ivermectin or pharmaceutically acceptable salt thereof.

The liquid pharmaceutical composition typically comprises isotonic agents. The isotonic agents may be any pharmaceutically acceptable isotonic agents. Suspensions will desirably be isotonic. The formulations which are used present process may be adjusted to desired isotonicity by the addition of suitable isotonic agents.

According to a preferred embodiment, the isotonic agent in the step numbered b) (ii) is selected from the group comprising mannitol, sodium chloride, potassium chloride and sodium bromide or a pharmaceutically acceptable salt thereof.

According to the preferred embodiment, the isotonic agents in the step numbered b) (ii) is sodium chloride.

Typically, the liquid pharmaceutical composition comprises one or more buffering agents. The buffering agents are pharmaceutically acceptable buffering agents. The buffering agents may be any buffering agents suitable for use in a liquid pharmaceutical composition suitable for inhalation. One or more buffering agents are typically selected from citrate or phosphate buffers. Citrate buffers is selected from the group comprising citric acid, sodium citrate and mixtures thereof. Phosphate buffers is selected from the group comprising phosphoric acid, monosodium phosphate, dibasic sodium phosphate and mixtures thereof.

According to one embodiment, the pharmaceutical composition comprises at least two buffering agents in the present invention.

According to one embodiment, the buffering agents is selected from the group comprising citric acid, sodium citrate, phosphoric acid, monosodium phosphate, dibasic sodium phosphate and mixtures thereof.

According to the preferred embodiment, the buffering agents in the step numbered b (ii) are monosodium phosphate dihydrate and dibasic sodium phosphate anhydrous.

The applied process steps have a direct effect on the blend uniformity, which is one of the first chemical indicators of the product's quality profile. It has been observed that if the above steps are not followed and are added only one dispersing or suspending agent into the present process, the blend uniformity cannot be achieved.

The steps of adding dispersing or suspending agents and their weight ratios of great importance in order to ensure homogenization and prevent losses in the process.

According to one embodiment, the pharmaceutical compositions subjected to the invention are prepared by these steps:

(i) heating the water for injection
(ii) adding respectively polysorbate 80 (polyoxyethylene (20) sorbitan monooleate), sorbitan monolaurate (span20) and mixing
(iii) adding ivermectin and mixing
b- obtaining Mixture 2 by:
(i) heating the water for injection
(ii) adding respectively sodium chloride, monosodium phosphate dihydrate and anhydrous dibasic sodium phosphate, and mixing
c- mixing the Mixture 1 and Mixture 2

wherein the temperature of water for injection is 45°C-55°C and the weight ratio of polysorbate 80 (polyoxyethylene (20), sorbitan monooleate) to sorbitan monolaurate (span20) is between 15:1- 5:1, preferably 12:1-5:1, more preferably 10:1-5:1.

The invention also defines suspension compositions obtained by the process subjected to the invention.

According to the preferred embodiment, a suspension composition comprises ivermectin or pharmaceutically acceptable salt thereof.

According to the preferred embodiment, a suspension composition comprises ivermectin.

According to the preferred embodiment, a suspension composition comprising ivermectin, isotonic agents, buffering agents, dispersing or suspending agents.

According to one embodiment, the amount of polysorbate 80 (polyoxyethylene (20) sorbitan monooleate) is between 0-0.5 % by weight of the total composition.

According to one embodiment, the amount of sorbitan monolaurate (span20) is between 0-0.2 % by weight of the total composition.

According to one embodiment, the amount of monosodium phosphate dihydrate is between 0-2.5 % by weight of the total composition.

According to one embodiment, the amount of dibasic sodium phosphate anhydrous is between 0-1.5 % by weight of the total composition.

According to one embodiment, the amount of sodium chloride is between 0-1 % by weight of the total composition.

According to one embodiment, the concentration of ivermectin in the pharmaceutical composition is , 0.25 mg/1 mL, 0.5 mg/1 mL, 1 mg/1 mL, 2 mg/1 mL and 5 mg/1 mL.

According to one preferred embodiment, the process for suspension composition for nebulization subjected to the invention comprises;

- ivermectin,
- polysorbate 80,
- sorbitan monolaurate,
- monosodium phosphate dihydrate,
- dibasic sodium phosphate anhydrous,
- sodium chloride,
- water for injection.

According to all these embodiments, the below-given formulations can be used process for preparing a suspension composition subjected to the invention. These examples are not limiting the scope of the present invention and should be considered under the light of the foregoing detailed disclosure.

Example 1:

Ingredients	Amount (mg)
Ivermectin	0.5 mg
Polysorbate 80	0.025 mg
Sorbitan monolaurate	0.003125 mg
Monosodium phosphate dihydrate	9.4 mg
Dibasic sodium phosphate anhydrous	1.75 mg
Sodium chloride	0.5 mg
Water for injection	1 mL

Example 2:

Ingredients	Amount (mg)
Ivermectin	1 mg
Polysorbate 20	0.025 mg
Sorbitan monolaurate	0.003125 mg
Monosodium phosphate dihydrate	9.4 mg
Dibasic sodium phosphate anhydrous	1.75 mg
Sodium chloride	0.5 mg
Water for injection	1 mL

Example 3:

Ingredients	Amount (mg)
Ivermectin	0.5 mg
Polysorbate 80	0.3125 mg
Sorbitan monolaurate	0.003125 mg
Monosodium phosphate dihydrate	9.4 mg
Dibasic sodium phosphate anhydrous	1.75 mg
Sodium chloride	0.5 mg
Water for injection	1 mL

According to a preferred embodiment, a suspension composition subjected to the invention is used in the treatment or the prophylaxis of of different infections especially COVID-19, SARS-CoV-2, SARS-CoV-2 infection.

CLAIMS

1. A process for the preparation of a homogeneous suspension to be used in pharmaceutical formulations for inhalation by nebulization, which comprises the following steps:

a- obtaining Mixture 1 by:

(i) heating the water for injection

(ii) adding respectively the first dispersing or suspending agent, the second dispersing or suspending agent and mixing

(iii) adding ivermectin and mixing

b- obtaining Mixture 2 by:

(i) heating the water for injection

(ii) adding respectively isotonic agent, and at least two buffering agents, and mixing

c- mixing the Mixture 1 and Mixture 2

wherein the temperature of water for injection is 45°C-55°C and the weight ratio of first dispersing or suspending agent to second dispersing or suspending agent is between 15:1-5:1, preferably 12:1-5:1, more preferably 10:1-5:1.

2. A process according to claim 1, wherein the first dispersing or suspending agent is selected from the group comprising polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), polysorbate 80 (polyoxyethylene (20) sorbitan monooleate), sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate (SpanR85), sorbitan mono-oleate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate or mixtures thereof.

3. A process according to claim 2, the first dispersing or suspending agent is polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

4. A process according to claim 1, wherein the second dispersing or suspending agent is selected from the group comprising polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate

60 (polyoxyethylene (20) sorbitan monostearate), sorbitan monolaurate (span 20), sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate (SpanR85), sorbitan mono-oleate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, polyethylene glycol 400 and glyceryl monolaurate or mixtures thereof.

5. A process according to claim 4, wherein the second dispersing or suspending agent is sorbitan monolaurate (span20).

6. A process according to any one of the proceeding claims, wherein the isotonic agent is selected from the group comprising mannitol, sodium chloride, potassium chloride and sodium bromide or a pharmaceutically acceptable salt thereof.

7. A process according to claim 6, the isotonic agent is sodium chloride.

8. A process according to any one of the proceeding claims, wherein buffering agents are selected from the group comprising citric acid, sodium citrate, phosphoric acid, monosodium phosphate, dibasic sodium phosphate and mixtures thereof.

9. A process according to claim 8, wherein buffering agents are monosodium phosphate dihydrate and dibasic sodium phosphate anhydrous.