Description

This invention relates to aqueous pharmaceutical suspension compositions. More particularly, the invention relates to a taste masked pharmaceutical suspension comprising substantially water insoluble pharmaceutical actives, suspension agents and taste masking agents and a process for making such taste masked liquid pharmaceutical suspensions.

Orally administered medicaments are given to the patient in many forms, including solid form such as capsules, caplets or tablets and liquid form such as solutions, emulsions or suspensions. Medicaments administered in solid form are usually intended to be swallowed whole, therefore, the often disagreeable taste of the active ingredient need not be taken into account in formulating the medicine, except for the provision of means to prevent the taste from being apparent during the short time the medicine is in the mouth. Such means may include the provision of an appropriately thin and quickly dissolving coating on a tablet or caplet or the use of a gelatin capsule form, (the gelatin outer shell of the capsule keeps the active ingredient inside until the capsule has been swallowed), or simply compressing a tablet firmly so that it will not begin to disintegrate during the short time that it is intended to be in the mouth.

Children, older persons, and many other persons including disabled or incapacitated patients have trouble swallowing whole tablets and even capsules. Therefore, in cases where the dosage to be administered cannot be made into a very small tablet or capsule, it is desirable to provide the medicine either in a chewable solid form or a liquid form. For many patients, including pediatric and geriatric patients, a liquid oral dosage form is preferable over chewable dosage form because of the ready swallowability without chewing of the liquid dosage form.

A common problem associated with liquid dosage forms is the often disagreeable taste of the active ingredients which manifest itself during the time that the liquid dosage form is in the mouth prior to swallowing. In some cases, the taste of the active medicament in a liquid form is generally overpowered by adding flavoring ingredients to the liquid so that when it is swallowed the bitter or unpleasant taste of the medicament is masked. For instance, this has been done with a pediatric liquid dosage form of acetaminophen (N-acetyl para-aminophenol or "APAP"). APAP is available commercially in an aqueous solution that includes overpowering flavor ingredients that masked the unpleasant taste of the APAP.

Aqueous solutions are generally stable and easy to prepare for water soluble actives, such as APAP, but it is difficult to prepare water insoluble pharmaceutical actives in storage stable ready-to-use liquid dosage form. Water insoluble ingredients present in water based solutions tend to separate or settle out and even shaking before administration does not insure a consistently accurate dosage regimen. While some water insoluble medicaments are soluble in alcohol, and may be presented in alcohol solutions, it is more desirable, particularly in pediatric dosage forms, to use aqueous "alcohol free" solutions.

EP-A-0298740 describes pediatric ibuprofen compositions wherein the ibuprofen remains in aqueous suspension and wherein the bitter taste of ibuprofen is masked. The suspension-stabilising combination of ingredients comprises from 1.00 to 1.50% w/v of the total composition and consists essentially of xanthan gum, microcrystalline cellulose, sodium carboxymethylcellulose and polysorbate 80. The taste-masking combination comprises 55% to 75% w/v of the total composition and consists essentially of sucrose and sorbitol solution. The compositions also contain citric acid as a flavour enhancer in an amount sufficient to adjust the pH to 3.5 to 5, and water qs to 100% by volume of the composition.

WO86/06626 describes a method of preparing microencapsulated drug formulations that will form stable suspensions in water. The drug particles are typically encapsulated in ethylcellulose or the like so as to mask the taste of the drug. The encapsulated drug particles are bound to particles of a thickening agent by means of a binder. The purpose of the thickening agent is to stabilize the resulting suspension of microencapsulated drug particles when the formulations are mixed with water. The thickening agent may be an alginate, carrageenan, agar-agar, tragacanth gum, xanthan gum, modified starch or the like. The binder is typically a cellulose derivative or polyvinylpyrrolidone.

The present invention is directed to discovery of a stable aqueous suspension system for water insoluble pharmaceutical actives which when combined with taste masking compositions achieve a palatable dosage form for both geriatric and especially pediatric applications.

The present invention provides an aqueous pharmaceutical suspension comprising: from 0.2% to 20.0% by weight by volume of a substantially water-insoluble pharmaceutical active; from 0.13 to 0.24% by weight by volume of xanthan gum; from 1.05 to 1.60% by weight by volume of pregelatinized starch; from 0.01 to 1.00 by weight by volume of polyoxyethylene sorbitan monooleate; an effective amount of a taste masking composition selected from the group consisting of sugar, sweet polyhydric alcohol, glycerin, artificial sweetener, flavoring agents and mixtures thereof; and water. The substantially water insoluble pharmaceutical active is preferably ibuprofen and preferably comprises 0.4% to 10% by weight by volume. In further

preferred embodiments of the invention the taste masking composition comprises from 20 to 35% sucrose, from 0 to 10% sorbitol and from 5 to 30% glycerin by weight by volume of the total suspension. Preferably citric acid, or a pharmaceutically acceptable salt thereof is added to the suspension in an amount to stabilize the pH of the solution at between 3.5 and 5.0.

As embodied and fully described herein the present invention also provides a process for preparing an aqueous pharmaceutical suspension composition comprising the steps of:

(a) dry blending from 0.13 to 0.24% xanthan gum, 1.05 to 1.60% pregelatinized starch and from 4% to 7% sugar, preferably sucrose, by weight by volume of the total suspension;

(b) separately mixing about 50% water, 5 to 30% glycerin, and 0 to 10% of a sweet polyhydric alcohol, preferably sorbitol, by weight by volume of the total suspension;

(c) adding the dry blend of step (a) with the aqueous mixture of step (b) and mixing until the xanthan gum and pregelatinized starch are uniformly dispersed throughout the mixture;

(d) adding from 16 to 28% sugar, preferably sucrose, by weight by volume of the total suspension to the dispersion of step (c) and mixing until the ingredients are uniformly dispersed in the mixture;

(e) admixing .01 to 1.00% polyoxyethylene sorbitan monooleate, and 0.2 to 20.0% of a substantially water insoluble pharmaceutical active by weight by volume of the total suspension and sufficient citric acid to stabilize the pH of the solution at between 3.5 to 5.0, with the mixture of step (d) until the ingredients are uniformly dispersed throughout the mixture; and

(f) mixing sufficient water to the mixture of step (e) to produce an aqueous pharmaceutical suspension of 100% desired volume.

The invention will now be described specifically in terms of its most preferred embodiments which is the preparation of aqueous suspensions of ibuprofen. Ibuprofen is a medicament used in both over-the-counter preparations and in prescription drugs for analgesic and antipyretic purposes. Ibuprofen is generally indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothaches, muscular aches, backache, for minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever. Reference will also be made in detail herein to other preferred embodiments of the compositions, processes and methods of the invention.

Aqueous suspension oral dosage forms for water insoluble or sparingly water soluble drugs are particularly advantageous since they can be alcohol free and provide an alternate means to tablets, caplets, and capsules for oral dosage. Ibuprofen is the most preferred water insoluble pharmaceutical active useful in accordance with the invention. Ibuprofen is substantially water insoluble at pH's below 6. For the purposes of the present invention the term substantially water insoluble refers to compositions which are insoluble, practically insoluble or only slightly soluble in water. This solubility can be at certain pH's e.g. 3.5 to 6 for ibuprofen, or cover a narrower or broader range of pH to determine water insolubility. Examples of other water insoluble pharmaceutical actives that can be used in accordance with the invention include but are not limited to the following examples: cardiovascular drugs, e.g. cardiac glycosides, clofibrate and probucol; hypoglycemic drugs; sedatives/hypnotics, e.g. barbiturates, disulfiram and glutethimide; antiepileptics, e.g., carbamazepine, mephenytoin, phenytoin and phensuximide; psycholpharmacologic agents e.g. perphenazine; analgesic, antipyretic and anti-inflammatory agents, e.g. naproxen, oxycodone, indomethacin, and phenylbutazone; antineoplastic drugs such as lomustine; and antimicrobials such as erythromycin estolate.

The aqueous pharmaceutical suspension composition in accordance with the present invention comprises from 0.2% to 20.0% of the substantially water insoluble pharmaceutical active. This amount is based in general terms on effective amounts of pharmaceutical actives such that suspensions containing less than 0.2% of pharmaceutical actives are possible. Amounts of pharmaceutical active in this range are generally acceptable for taste masking but it is possible that more than 20% of a water insoluble pharmaceutical active could be included in the suspension and be sufficiently taste masked for consumer acceptability.

Stabilizing the suspension of water insoluble pharmaceutical actives is the key inventive step of the present invention. It has been found by the present inventor , that the unique combination of xanthan gum, pregelatinized starch and a surfactant such as polyoxyethylene sorbitan monooleate produces advantageously storage stable and homogeneously dispersed suspensions of water insoluble pharmaceutical actives.

Xanthan gum is a high molecular weight natural carbohydrate, specifically, a polysaccharide. Xanthan gum is a known suspension stabilizer by itself for suspending fruit pulp in drinks and concentrates, calamine lotions, preventing settling in food toppings, salad dressings and syrups.

Pregelatinized starch is prepared from modified, stabilized and waxy, maize food starch. Pregelatinized starch is precooked so that it swells and begins to thicken instantly when added to cold water. The pregelatinized starch component used in combination with xanthan gum in accordance with the present

invention has been found to provide superior storage stable and homogeneously dispersed suspensions of water insoluble pharmaceutical actives.

The surfactant used in accordance with the invention is polyoxyethylene sorbitan monooleate, also known as polysorbate 80. Such surfactants or surface active molecules consist of two ends or parts: a polar or ionic group at one end and a non-polar organic chain at the other end. Each part of the surfactant has an affinity for a different phase of the aqueous suspension. Once wetted by the aqueous phase, the surfactant provides stability by what is known as steric stabilization. The non-polar group adsorbs onto the non-wetting hydrophobic surface of the solid phase and the polar end extends into the aqueous phase. This dual absorption allows the suspended particles to be surrounded by water molecules and incorporated into the aqueous solution. In accordance with the present invention the suspension is stabilized by a mixture of suspension stabilizing effective amounts of xanthan gum, preglatinized starch and polyoxyethylene sorbitan monooleate. Preferably the suspension stabilizing effective amount of these components comprises from about 1.25 to about 1.90% weight by volume of the total suspension. In particular, the xanthan gum comprises 0.13 to 0.24%, the preglatinized starch 1.05 to 1.60%, and the polyoxyethylene sorbitan monooleate 0.01 to 1.00% weight by volume of the total suspension.

Taste masking components generally comprise from 25 to 50% by weight by volume of the total composition. The present invention however is not limited to this amount but rather to an effective amount of the taste masking composition to produce a consumer acceptable suspension. For example, if highly intense artificial sweeteners are used a lesser amount would be required then would be the case for sugars to achieve effective taste masking. The amount of taste masking required would vary with the amount of pharmaceutical active used as well as the intensity of the poor taste of the pharmaceutical active. If a particular pharmaceutical active is substantially taste neutral then the amount of taste masking composition required could be greatly reduced.

Preferred taste masking compositions in accordance with the invention include but are not limited to sugars, sweet polyhydric alcohols, glycerin, artificial sweetener, flavoring agents and mixtures thereof. Examples of sugars include sucrose, fructose, dextrose, and glucose. Examples of sweet polyhydric alcohols include sorbitol and mannitol. The type of glycerin preferably used is U.S.P. grade. Examples of artificial sweetners include aspartame, sucralose, cyclamates, saccharin and mixtures thereof. Examples of flavoring agents include natural and artificial fruit flavors.

Citric acid is a preferred ingredient to add to the suspension to stabilize the pH of the suspension at between 3.5 and 5.0. Citric acid is advantageously added since a lower pH (i.e. 3.5 to 5.0) will prevent microbial growth and add to the stability of the product. A preferred pH for the suspension when ibuprofen is the substantially water insoluble pharmaceutical active used is between 3.5 and 5.0 since the ibuprofen will remain water insoluble and in suspension at this microbial inhibiting pH.

The present invention also provides a process for preparing the aqueous pharmaceutical suspension composition. The preferred process comprises the following sequential steps:

(a) dry blending from 0.13 to 0.24% xanthan gum, 1.05 to 1.60% pregelatinized starch and from 4% to 7% sugar, preferably sucrose, by weight by volume of the total suspension;

(b) separately mixing about 50% water, 5 to 30% glycerin, and 0 to 10% of a sweet polyhydric alcohol, preferably sorbitol, by weight by volume of the total suspension;

(c) adding the dry blend of step (a) with the aqueous mixture of step(b) and mixing until the xanthan gum and pregelatinized starch are uniformly dispersed throughout the mixture;

(d) adding from 16 to 28% sugar, preferably sucrose, by weight by volume of the total suspension to the dispersion of step (c) and mixing until the ingredients are uniformly dispersed in the mixture;

(e) admixing .01 to 1.00% polyoxyethylene sorbitan monooleate, 0.2 to 20.0% preferably 0.4 to 10.0% of a substantially water insoluble pharmaceutical active, preferably ibuprofen by weight by volume of the total suspension and sufficient citric acid to lower the pH of the solution to between 3.5 to 5.0 to the mixture of step (d) until the ingredients are uniformly dispersed throughout the mixture; and

(f) adding and mixing sufficient water to the mixture of step (e) to produce an aqueous pharmaceutical, preferably ibuprofen, suspension of 100% desired volume.

In preferred embodiments of the process an effective amount of preservative such as, for example, benzoic acid, and its salts including sodium benzoate, or sorbic acid and its salts, is added to the mixture in step (e) and the suspension in step (f) is subjected to a deaerating step so that the volume of the suspension is adjusted to 100% by addition of water after such deaerating. Preferably the flavoring and coloring ingredients added to the mixture in step (e) are of the type and amount desired for the particular suspension to meet the preferences dictated by the intended consumer of such suspension e.g. pediatric or adult. A more detailed example of the preferred process of the invention as carried out with ibuprofen and tolmetin as the active ingredients is provided in the following examples section.

Examples

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a preferred process for preparing the compositions of the invention.

Example 1 - Ibuprofen Suspension Liquid Dosage Form

Ingredients	Unit Amount (gm.%)	Batch Amount (grams)
Ibuprofen, USP	2.0	7570.0
Glycerin, USP	10.0	37850.0
Sucrose, Granular, NF, (Beet)	30.0	113550.0
Pregelatinized Starch (CLEARJEL®)	1.31	4958.40
Xanthan Gum, NF, (KELTROL-T®)	0.18	681.30
Polysorbate 80, NF, (TWEEN 80®)	0.05	189.25
Citric Acid, anhydrous, USP	0.18	681.30
Sodium Benzoate, NF	0.20	757.0
Artificial Flavorings	0.43	1627.55
FD&C Yellow #10	0.0025	9.463
FD&C Red #40	0.0009	3.407
Purified Water, USP qs to:	100.00 ml.	378.5 Liters

PROCESSING DIRECTIONS

1. Dry blend in a suitable blender, 20% granular sucrose (22.53 kg.) with the pregelatinized starch and xanthan gum, for 10 minutes.
2. To a tared pot, add 200.0 liters of purified water and glycerin, and mix approximately 2-3 minutes.
3. Add the dry blend mixture, (gums and sucrose), and mix until gums are dispersed, approximately 10-15 minutes.
4. Add the remaining sucrose, (90.72 kg.), and mix until dissolved, approximately 10-15 minutes. Take in-process viscosity 1.9664 N s/m^2(1966.4 cps.)
5. Add polysorbate 80, citric acid and sodium benzoate and mix approximately 5-10 minutes.
6. Add ibuprofen (screened through 40 mesh), and mix approximately 15 minutes.
7. Add flavors and mix approximately 5 minutes.
8. Add dyes, FD&C red #40, and FD&C Yellow #10, (premixed in purified water,), and mix approximately 5 minutes.
9. Bring suspension to near final volume with 56.7 liters purified water, and mix approximately 10 minutes.
10. Let suspension deaerate overnight, approximately 12-16 hours.
11. Bring suspension to final volume with 10.6 liters purified water, and mix approximately 10 minutes.

The above produces a batch size of approximately 378.5 liters or 100 gallons of ibuprofen suspension (100mg/5ml) at a pH of 3.97.

Example 2 - Preparation of Ibuprofen Suspension Liquid Drop Dosage Form

Ingredients	Unit Amount (gm.%)	Batch Amount (grams)
Ibuprofen, USP	4.0	15140.0
Glycerin, USP	5.0	18925.0
Sorbitol Solution	5.0	18925.0
Sucrose, Granular, NF (Beet)	30.0	113550.0
Pregelatinized Starch (CLEARJEL)	1.2	4542.0
Xanthan Gum, NF, (Keltrol-T)	0.2	757.0
Polysorbate NF (TWEEN 80)	0.05	189.25
Citric Acid, anhydrous, USP	0.18	681.30
Sodium Benzoate, NF	0.20	757.0
Artificial Flavorings	0.86	3255.1
FD&C Red #40	0.001	3.785
Purified Water, USP qs to:	100.0	378.5
Liters		

PROCESSING DIRECTIONS

1. Dry blend in a suitable blender, 20% granular sucrose, (22.83 kg.) with the pregelatinized starch and the xanthan gum for 10 minutes.
2. To a tared pot, add 193.5 liters of purified water glycerin and sorbitol solution, and mix approximately 2-3 minutes.
3. Add the dry blend mixture (gums and sucrose), and mix until gums are dispersed, approximately 10-15 minutes.
4. Add the remaining sucrose, (90.72 kg.), and mix until dissolved, approximately 10-15 minutes. Take in-process viscosity 1.5132 N s/m^2 (1513.2 cps).
5. Add polysorbate 80, citric acid, sodium benzoate, and mix approximately 5-10 minutes.
6. Add ibuprofen (screened through 40 mesh) and mix approximately 15 minutes.
7. Add flavors and mix approximately 5 minutes.
8. Add FD&C Red #40 dye, premixed in purified water and mix approximately 5 minutes.
9. Bring suspension to near final volume with 47.6 liters purified water and mix approximately 10 minutes.
10. Let suspension deaerate overnight, approximately 12-16 hours.
11. Bring suspension to final volume with 12.2 liters purified water USP, and mix approximately 10 minutes.

The above produces a batch size of 378.5 Liters ibuprofen suspension drops (40 mg/ml) at a pH of 3.92.

Example 3 - Tolmetin Liquid Suspension Dosage Form

The process of Example 1 is carried out except that 7.570 kg. of tolmetin is substituted for ibuprofen to produce 100 mg/5ml tolmetin suspension.

The scope of the present invention is not limited by the examples herein. For example, additional medicaments may be added to the aqueous suspension to provide a combination medication. Further, the pharmaceutical suspension of the invention may be utilized for non-medicament ingredients including nutrients such as vitamins and minerals.

Application of the compositions and method of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the present application cover the modifications and variations of this invention provided that they come within the scope of the appended claims.

* C L M S *

Claims

1. An aqueous pharmaceutical suspension comprising:
from 0.2% to 20.0% by weight by volume of a substantially water-insoluble pharmaceutical active;
from 0.13 to 0. 24% by weight by volume of xanthan gum;
from 1.05 to 1.60% by weight by volume of pregelatinized starch;
from 0.01 to 1.00% by weight by volume of polyoxyethylene sorbitan monooleate;
an effective amount of a taste masking composition selected from the group consisting of sugar, sweet polyhydric alcohol, glycerin, artificial sweetener, flavoring agents and mixtures thereof; and
water

2. A suspension according to claim 1, wherein the xanthan gum, pregelatinized starch and polyoxyethylene sorbitan monooleate taken together comprise from 1.25 to 1.90% by weight by volume of the total suspension.

3. A suspension according to claim 1 or 2, wherein the taste masking composition comprises from 25 to 50% by weight by volume of the total suspension.

4. A suspension according to any of claims 1 to 3, wherein the taste masking composition comprises from 20 to 35% sucrose, from 0 to 10% sorbitol and from 5 to 30% glycerin by weight by volume of the total suspension.

5. A suspension according to any of claims 1 to 4, wherein citric acid is added to the suspension in an amount to stabilize the pH of the solution at between 3.5 and 5.0.

6. A suspension according to any of claims 1 to 5, wherein the pharmaceutical active is ibuprofen.

7. A suspension according to claim 6 wherein the suspension comprises from 0.4% to 10% by weight by volume of the ibuprofen.

8. The suspension of claim 7, comprising about 2.0% ibuprofen, 0.18% xanthan gum, 1.31% pregelatinized starch and 0.05% polyoxyethylene sorbitan monooleate by weight by volume of the total suspension.

9. A process for producing the suspension according to any of claims 1 to 8, which comprises mixing together the ingredients until they are uniformly dispersed throughout the mixture and, if necessary, adjusting to the desired volume.

10. A process for preparing an aqueous pharmaceutical suspension comprising the steps of:
(a) dry blending from 0.13 to 0.24% xanthan gum, from 1.05 to 1.60% pregelatinized starch and from 4% to 7% sugar by weight by volume of the total suspension;
(b) separately mixing about 50% water, 5 to 30% glycerin, and 0 to 10% of a sweet polyhydric alcohol by weight by volume of the total suspension;
(c) adding the dry blend of step (a) with the aqueous mixture of step (b) and mixing until the xanthan gum and pregelatinized starch are uniformly dispersed throughout the mixture;
(d) adding from 16 to 28% sugar by weight by volume of the total suspension to the dispersion of step (c) and mixing until the ingredients are uniformly dispersed in the mixture;
(e) mixing 0.01 to 1.00% polyoxyethylene sorbitan monooleate and 0.2 to 20.0% of a substantially water insoluble pharmaceutical active by weight by volume of the total suspension to the mixture of step (d) until the ingredients are uniformly dispersed throughout the mixture; and
(f) mixing sufficient water to the mixture of step (e) to produce an aqueous pharmaceutical suspension of 100% desired volume.

11. A process according to claim 10, wherein sufficient citric acid to stabilize the pH of the solution at between 3.5 to 5.0 is added to the mixture in step (e).

12. A process according to claim 10 or 11, wherein an effective amount of preservative is added to the mixture in step (e).

13. A process according to any of claims 10 to 12, wherein the pharmaceutical active added in step (e) is ibuprofen at a level of 0.4 to 10% by weight by volume of the total suspension.

14. A process of any one of claims 10 to 13, wherein the sugar added in steps (a) and (d) is sucrose.

Patentansprüche

1. Wäßrige pharmazeutische Suspension, umfassend:
   von 0,2 % bis 20,0 %, bezogen auf Gewicht pro Volumen, eines im wesentlichen wasserunlöslichen pharmazeutischen Wirkstoffs;
   von 0,13 bis 0,24 %, bezogen auf Gewicht pro Volumen, Xanthangummi;
   von 1,05 bis 1,60 %, bezogen auf Gewicht pro Volumen, prägelatinisierte Stärke;
   von 0,01 bis 1,00 %, bezogen auf Gewicht pro Volumen, Polyoxyethylensorbitanmonooleat;
   eine wirksame Menge einer geschmacksmaskierenden Zusammensetzung, ausgewählt aus der Gruppe bestehend aus Zucker, süßem mehrwertigen Alkohol, Glycerin, künstlichem Süßstoff, Geschmacksstoffen und Gemischen davon; und
   Wasser.

2. Suspension nach Anspruch 1, in der der Xanthangummi, prägelatinisierte Stärke und Polyoxyethylensorbitanmonooleat zusammengenommen von 1,25 bis 1,90 %, bezogen auf Gewicht pro Volumen der gesamten Suspension, umfassen.

3. Suspension nach Anspruch 1 oder 2, in der die geschmacksmaskierende Zusammensetzung von 25 bis 50 %, bezogen auf Gewicht pro Volumen der gesamten Suspension, umfaßt.

4. Suspension nach einem der Ansprüche 1 bis 3, in der die geschmacksmaskierende Zusammensetzung von 20 bis 35 % Sucrose, von 0 bis 10 % Sorbit und von 5 bis 30 % Glycerin, bezogen auf Gewicht pro Volumen der gesamten Suspension, umfaßt.

5. Suspension nach einem der Ansprüche 1 bis 4, in der Zitronensäure zu der Suspension in einer Menge zugefügt wird, die den pH der Lösung zwischen 3,5 und 5,0 stabilisiert.

6. Suspension nach einem der Ansprüche 1 bis 5, in der der pharmazeutische Wirkstoff Ibuprofen ist.

7. Suspension nach Anspruch 6, in der die Suspension von 0,4 % bis 10 %, bezogen auf Gewicht pro Volumen, Ibuprofen umfaßt.

8. Suspension nach Anspruch 7, umfassend etwa 2,0 % Ibuprofen, 0,18 % Xanthangummi, 1,31 % prägelatinisierte Stärke und 0,05 % Polyoxyethylensorhitanmonooleat, bezogen auf Gewicht pro Volumen der gesamten Suspension.

9. Verfahren zum Herstellen der Suspension nach einem der Ansprüche 1 bis 8, umfassend das Zusammenmischen der Bestandteile, bis sie in dem Gemisch gleichförmig dispergiert sind, und, falls notwendig, Einstellen auf das gewünschte Volumen.

10. Verfahren zur Herstellung einer wäßrigen pharmazeutischen Suspension, umfassend die Schritte:
   (a) trockenes Mischen von 0,13 bis 0,24 % Xanthangummi, von 1,05 bis 1,60 % prägelatinisierte Stärke und von 4 % bis 7 % Zucker, bezogen auf Gewicht pro Volumen der gesamten Suspension;
   (b) getrenntes Mischen von etwa 50 % Wasser, 5 bis 30 % Glycerin und 0 bis 10 % eines süßen mehrwertigen Alkohols, bezogen auf Gewicht pro Volumen der gesamten Suspension;
   (c) Zugehen der trockenen Mischung aus Schritt (a) zu dein wäßrigen Gemisch von Schritt (b) und Mischen, bis der Xanthangummi und die prägelatinisierte Stärke in dem Gemisch gleichförmig dispergiert sind;
   (d) Zugeben von 16 bis 28 % Zucker, bezogen auf Gewicht pro Volumen der gesamten Suspension, zu der Dispersion von Schritt (c) und Mischen, bis die Bestandteile in dem Gemisch gleichförmig dispergiert sind;
   (e) Mischen von 0,01 bis 1,00 % Polyoxyethylensorbitanmonooleat und 0,2 bis 20,0 % eines in wesentlichen wasserunlöslichen pharmazeutischen Wirkstoffs, bezogen auf Gewicht pro Volumen

der gesamten Suspension, zu dem Gemisch von Schritt (d) bis die Bestandteile in dem Gemisch gleichförmig dispergiert sind; und
(f) Mischen einer ausreichenden Menge Wasser zu dein Gemisch von Schritt (e), um eine wäßrige pharmazeutische Suspension von 100 % gewünschten Volumen herzustellen.

11. Verfahren nach Anspruch 10, in dem eine ausreichende Menge Zitronensäure zu dem Gemisch in Schritt (e) zugegeben wird, um den pH der Lösung zwischen 3,5 und 5,0 zu stabilisieren.

12. Verfahren nach Anspruch 10 oder 11, in dem eine wirksame Menge eines Konservierungsmittels zu dem Gemisch in Schritt (e) zugegeben wird.

13. Verfahren nach einem der Ansprüche 10 bis 12, in dem der pharmazeutische Wirkstoff, der in Schritt (e) zugegeben wird: Ibuprofen in einer Konzentration von 0,4 bis 10 %, bezogen auf Gewicht pro Volumen der gesamten Suspension, ist.

14. Verfahren nach einem der Ansprüche 10 bis 13, in dem der in den Schritten (a) und (d) zugefügte Zucker Sucrose ist.

Revendications

1. Suspension pharmaceutique aqueuse comprenant :
0,2% à 20,0% en poids par volume d'un agent actif pharmaceutique essentiellement insoluble dans l'eau;
0,13 à 0,24% en poids par volume de gomme xanthane;
1,05 à 1,60% en poids par volume d'amidon prégélatinisé;
0,01 à 1,00% en poids par volume de monooléate de polyoxyéthylène sorbitan;
une quantité efficace d'une composition masquant le goût, choisie dans le groupe consistant en sucre, alcool polyhydrique doux, glycérine, édulcorant artificiel, agents arômatisants et leurs mélanges; et
de l'eau

2. Suspension selon la revendication 1 où la gomme xanthane, l'amidon prégélatinisé et le monooléate de polyoxyéthylène sorbitan pris ensemble forment 1,25 à 1,90% en poids par volume de la suspension totale.

3. Suspension selon la revendication 1 ou 2, où la composition masquant le goût forme 25 à 50% en poids par volume de la suspension totale.

4. Suspension selon l'une quelconque des revendications 1 à 3, où la composition masquant le goût contient 20 à 35% de saccharose, 0 à 10% de sorbitol et 5 à 30% de glycérine, en poids par volume de la suspension totale.

5. Suspension selon l'une quelconque des revendications 1 à 4, où on ajoute de l'acide citrique à la suspension, en une quantité pour stabiliser le pH de la solution entre 3,5 et 5,0.

6. Suspension selon l'une quelconque des revendications 1 à 5, où l'agent actif pharmaceutique est ibuprofène.

7. Suspension selon la revendication 6, où la suspension contient 0,4% à 10% en poids par volume d'ibuprofène.

8. Suspension de la revendication 7, comprenant environ 2,0% d'ibuprofène, 0,18% de gomme xanthane, 1,31% d'amidon prégélatinisé et 0,05% de monooléate de polyoxyéthylène sorbitan en poids par volume de la suspension totale.

9. Procédé de production de la suspension selon l'une quelconque des revendications 1 à 8, qui consiste à mélanger les ingrédients jusqu'à ce qu'ils soient uniformément dispersés dans tout le mélange et, si nécessaire, à ajuster au volume souhaité.

10. Procédé de préparation d'une suspension pharmaceutique active comprenant les étapes de :
(a) mélanger à sec 0,13 à 0,24% de gomme xanthane, 1,05 à 1,60% d'amidon prégélatinisé et 4% à 7% de sucre en poids par volume de la suspension totale.
(b) mélanger séparément environ 50% d'eau, 5 à 30% de glycérine et 0 à 10% d'un alcool polyhydrique doux en poids par volume de la suspension totale;
(c) ajouter le mélange sec de l'étape (a) au mélange aqueux de l'étape (b) et mélanger jusqu'à ce que la gomme xanthane et l'amidon prégélatinisé soient uniformément dispersés dans tout le mélange.
(d) ajouter 16 à 28% de sucre en poids par volume de la suspension totale à la dispersion de l'étape (c) et mélanger jusqu'à ce que les ingrédients soient uniformément dispersés dans le mélange;
(e) mélanger 0,01 à 1,00% de monooléate de polyoxyéthylène sorbitan et 0,2 à 20,0% d'un agent actif pharmaceutique essentiellement insoluble dans l'eau, en poids par volume de la suspension totale, au mélange de l'étape (d) jusqu'à ce que les ingrédients soient uniformément dispersés dans tout le mélange; et
(f) mélanger suffisamment d'eau au mélange de l'étape (d) pour donner une suspension pharmaceutique aqueuse de 100% du volume souhaité.

11. Procédé selon la revendication 10, où l'on ajoute, au mélange de l'étape (e), suffisamment d'acide citrique pour stabiliser le pH de la solution entre 3,5 et 5,0.

12. Procédé selon la revendication 10 ou 11, où on ajoute une quantité efficace d'un conservateur au mélange de l'étape (e).

13. Procédé selon l'une quelconque des revendications 10 à 12, où l'agent actif pharmaceutique ajouté à l'étape (e) est ibuprofène à un niveau de 0,4 à 10% en poids par volume de la suspension totale.

14. Procédé selon l'une quelconque des revendications 10 à 13, où le sucre ajouté aux étapes (a) et (d) est le saccharose.

* C L M S *