

Clarke, Modet & C^o
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 2860/PCT.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

Ref.: Expediente No. **05-091.231**
Solicitud de Patente a nombre de
Novartis AG.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
05-091.231-00004-0000
Dep. 2020 NULCREACIONE
Eve: 379 FASENACIONALII
Folios: 4

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Novartis AG.**, con domicilio en Basilea, Suiza, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial los recibos Nos. 07 - 97,244 de 28 de noviembre de 2007, 07 - 97,243 de 28 de noviembre de 2007 y 07 - 96,371 de 26 de noviembre de 2007, por la suma de \$202.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68.228

67

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-091231- -00004-0000

RECIBO OFICIAL DE CAJA : 07 - 97,244
FECHA : NOVIEMBRE 28 DE 2007

RECIBO OFICIAL DE CAJA : 07 - 97,244 Dep. 2020 NUECREACIONES
FECHA : NOVIEMBRE 28 DE 2007 Dep. 2020 NULACIONALII

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	72395998	28/11/2007	8,640,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		83 INVOCACION DE UNA PRIORIDAD EN SI	88,000.00
		TOTAL :	\$ 88,000.00

SON: SESENTA Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

18
62

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 97,243
FECHA : NOVIEMBRE 28 DE 2007

SE
NACIONALII

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	72395998	28/11/2007	8,640,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		83 INVOCACION DE UNA PRIORIDAD EN SI	68,000.00
		TOTAL :	\$ 68,000.00

SON: SESENTA Y OCHO MIL PESOS

4

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 96,371
FECHA : NOVIEMBRE 26 DE 2007

00000-0000

Dep. 2020 NUECREACION
Lve. 379 FASENACIONALII
Folios: 4

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	53267311	26/11/2007	28,480,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		83 INVOCACION DE UNA PRIORIDAD EN SI	68,000.00
		TOTAL :	\$ 68,000.00

SESENTA Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-91231

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577**

DE FECHA **29 DE JUNIO DEL 2007**, EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE SEPTIEMBRE DEL 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐

NO ☒



US 20020028794A1

71
77(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0028794 A1**
Brubaker et al. (43) **Pub. Date: Mar. 7, 2002**(54) **MEGESTROL ACETATE SUSPENSION**(57) **ABSTRACT**(76) Inventors: **Greg Allen Brubaker**, Sunbury, OH
(US); **Mahendra Dedhiya**, Nanuet, NY
(US); **Thomas Dean Mahon**, West
Jefferson, OH (US)An oral pharmaceutical composition in the form of a stable
suspension in water, said composition comprising:Correspondence Address:
BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P O BOX 368
RIDGEFIELD, CT 06877 (US)(a) about 10 to 200 mg per ml of micronized megestrol
acetate;(b) about 0.04 to 0.4% weight/volume of a wetting
agent; and(c) about 1.2 to 1.8% weight/volume of a suspending
agent,(21) Appl. No.: **09/864,841**(22) Filed: **May 24, 2001****Related U.S. Application Data**(63) Non-provisional of provisional application No.
60/219,822, filed on Jul. 21, 2000.**Publication Classification**(51) Int. Cl.⁷ **A61K 31/57**(52) U.S. Cl. **514/177**wherein said composition contains less than about 1.0%
weight/volume of propylene glycol and does not contain
polysorbate, polyethylene glycol, glycerol or sorbitol. The
pH of the suspension can be controlled with an appropriate
buffer system. In a preferred embodiment, the suspension
has a pH of greater than about 3.3. The oral pharmaceutical
composition is useful in the treatment of anorexia, cachexia
or significant weight loss resulting from or associated with
acquired immunodeficiency syndrome (AIDS).

MEGESTROL ACETATE SUSPENSION

RELATED APPLICATIONS

[0001] Benefit of U.S. Provisional Application Serial No. 60/219,822, filed on Jul. 21, 2000, is hereby claimed.

FIELD OF THE INVENTION

[0002] The present invention relates to a pharmaceutical composition containing megestrol acetate, which is the generic name for 17- α -acetyloxy-6-methylpregna-4,6 diene-3,20-dione. The pharmaceutical composition is in the form of a stable suspension in water, and is useful in the treatment of anorexia, cachexia or significant weight loss resulting from or associated with acquired immunodeficiency syndrome (AIDS).

BACKGROUND OF THE INVENTION

[0003] Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone, progesterone. The megestrol acetate oral suspension Megace® (Bristol Myers Squibb Corp.) contains micronized megestrol acetate (40 mg/mL), polysorbate 80, polyethylene glycol, water and other conventional additives to form a flocculated suspension. Megace® oral suspension is currently approved for use in the treatment of anorexia, cachexia, or an unexplained, significant weight loss in patients with a diagnosis of acquired immunodeficiency syndrome (AIDS). It is desirable to have an oral liquid dosage form available to treat this patient group who may have difficulty swallowing tablets or capsules or where a high dose would require the ingestion of a relatively large number of tablets or capsules.

[0004] Megestrol acetate is insoluble in water therefore an oral suspension formulation is practical. According to Remington's Pharmaceutical Sciences (Chapter 21, page 313), a pharmaceutical suspension may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Furthermore, a well formulated suspension should meet the following criteria. The dispersed particles should be of a size that they do not settle rapidly. If sedimentation occurs, however, the sediment must not form a hard cake but must be redispersible with a minimum of effort, i.e., a flocculated suspension. The product should also be easy to pour, pleasant to take, and resistant to microbial attack.

[0005] Possible concerns associated with the manufacture of suspensions are adequate dispersion of the particles in the vehicle, settling of the dispersed particles, and ultimate caking of the particles in the sediment making the suspension resistant to redispersion. In addition, the dissolution of the active drug substance and in vivo bioavailability is critical for a suspension dosage form and may be affected by the ingredients contained in the finished drug product. It is therefore desirable to define a formulation and process to address the issues described above to produce a pharmaceutically elegant oral suspension dosage form of megestrol acetate.

[0006] Kirk et al, U.S. Pat. No. 3,356,573, disclose a megestrol acetate pharmaceutical tablet preparation comprising lactose, magnesium stearate and starch. Kirk, et al, also disclose that liquid compositions of megestrol acetate can be useful but provided no details as to the composition of such formulations.

[0007] Petrow et al, U.S. Pat. No. 4,396,615, disclose a method of treating androgen-related disorders by administering 6-methyleneprogesterone derivatives concurrently with megestrol acetate. However, Petrow, et al. do not elaborate on what constitutes the megestrol acetate formulation.

[0008] Greaney et al., U.S. Pat. No. 4,370,321, disclose adjuvant therapy for the treatment of breast cancer employing megestrol acetate. However, the type or composition of the megestrol acetate formulation is not specifically described.

[0009] Labrie, U.S. Pat. No. 4,666,885, discloses combination therapy for treatment of female breast cancer comprising the administration of luteinizing hormones in combination with an anti-androgen compound such as megestrol acetate. In particular, Labrie discloses that the anti-androgens are formulated with conventional pharmaceutical excipients (e.g., spray dried lactose and magnesium stearate) into tablets or capsules for oral administration.

[0010] Labrie, U.S. Pat. No. 4,760,053 discloses methods of treating sex steroid dependent cancers by combination therapy which includes the use of megestrol acetate. However, Labrie does not describe the type or composition of pharmaceutical formulation used in the treatment.

[0011] Labrie, U.S. Pat. No. 4,775,661, discloses methods of treating female breast cancer with a combination therapy in which megestrol acetate is disclosed as a suitable steroidal anti-androgen. Labrie also discloses that megestrol acetate, as an active substance, may be mixed with lubricants such as polyethylene glycol and may include taste improving substances and can be worked into tablets or dragee cores.

[0012] Atzinger et al., U.S. Pat. No. 5,338,732, disclose an oral pharmaceutical composition of megestrol acetate in the form of a stable flocculated suspension of megestrol acetate in water. The flocculated suspension in Atzinger, et al, comprises megestrol acetate at a concentration of 15 to 150 mg/mL, in combination with a polysorbate at a concentration of 0.005% to 0.015% weight/volume (w/v) and a polyethylene glycol at a concentration greater than 5% w/v. Atzinger, et al., point out the distinction between a flocculated suspension and suspensions in general and point out that the stability of a flocculated suspension of a steroid such as megestrol acetate can be critically dependent on concentration.

[0013] Atzinger, et al., also disclose that megestrol acetate flocculated suspensions are unique because what would otherwise be predictable based on the prior art teachings does not apply when the drug is megestrol acetate. For instance, it is well known in the art prior to Atzinger et al. that megestrol acetate, a hydrophobic solid, is not easily wetted by water and has a relatively high interfacial tension accentuated by entrapped air absorbed on the surface of the particle. Hence, the use of surfactants are required to provide a suspension and maintain physical stability. According to Atzinger et al., the amount and type of surfactants are particularly critical in providing a stable flocc. The flocculated suspension of megestrol acetate of Atzinger et al. uses megestrol acetate micronized so that 90% of the weight of particles is below 20 microns and the mass median diameter is between 3.0 and 10 microns, and requires that the micronized particles are dispersed in water with polysorbate and

polyethylene glycol to reduce interfacial tension between the particle, entrapped gas and water.

[0014] Atzinger et al., discloses that in order to achieve a stable flocculated megestrol acetate suspension, polysorbate must be used at a concentration at about or less than 0.02% w/v, preferably from 0.005% to 0.015% w/v and most preferably 0.01% w/v, in combination with polyethylene glycol. At polysorbate 80 concentrations as low as 0.025% w/v, there is significant deflocculation and caking. They also state that at polysorbate concentrations at or below 0.005-0.01% w/v, a physically stable product was obtained but there is increased difficulty with respect to wetting of the micronized megestrol acetate at these low concentrations. Atzinger et al. further state that only surfactants having properties similar to polysorbate 80 can also be used. In this regard, they list polysorbate 20, 40, 60, 65 and 85 as having acceptable wetting properties.

[0015] Ragunathan, et al., U.S. Pat. No. 6,028,065, also disclose a stable flocculated suspension of megestrol acetate, but using a different formulation than that described in Atzinger. Specifically, Ragunathan, et al. disclose a stable flocculated suspension in water comprising:

[0016] a) megestrol acetate;

[0017] b) at least one compound selected from polyethylene glycol, propylene glycol, glycerol and sorbitol; and

[0018] c) a surfactant.

[0019] wherein polysorbate and polyethylene glycol are not simultaneously present in the composition. Ragunathan discloses that the compound selected from polyethylene glycol, propylene glycol, glycerol and sorbitol is preferably used at a concentration of up to 40% w/v, more preferably 5 to 30%, and most preferably 10 to 25%, and that the surfactant is preferably used at a concentration of about 0.0001 to 0.03% w/v. Ragunathan also discloses the use of a suspending agent (xanthan gum), preferably at a concentration of about 0.1 to 0.35% w/v, more preferably about 0.15 to 0.25%.

[0020] There exists a continuing need in the art for pharmaceutically elegant and stable oral suspension dosage forms of megestrol acetate.

SUMMARY OF THE INVENTION

[0021] The present invention provides a pharmaceutically elegant and stable oral suspension dosage form of megestrol acetate that is different from known formulations and provides acceptable in-vitro dissolution performance.

[0022] In one embodiment, the present invention is directed to an oral pharmaceutical composition in the form of a stable suspension in water, said composition comprising:

[0023] (a) about 10 to 200 mg per ml of micronized megestrol acetate;

[0024] (b) about 0.04 to 0.4% weight/volume of a wetting agent; and

[0025] (c) about 1.2 to 1.8% weight/volume of a suspending agent,

[0026] wherein said composition contains less than about 1.0% weight/volume of propylene glycol and does not contain polysorbate, polyethylene glycol, glycerol or sorbitol. The pH of the suspension can be controlled with an appropriate buffer system. In a preferred embodiment, the suspension has a pH of at least about 3.3.

[0027] The oral pharmaceutical composition of the present invention is useful in the treatment of anorexia, cachexia or significant weight loss resulting from or associated with acquired immunodeficiency syndrome (AIDS).

DETAILED DESCRIPTION OF THE INVENTION

[0028] The present invention is directed to an oral pharmaceutical composition in the form of a stable suspension in water, said composition comprising:

[0029] (a) about 10 to 200 mg per ml of micronized megestrol acetate;

[0030] (b) about 0.04 to 0.4% weight/volume of a wetting agent; and

[0031] (c) about 1.2 to 1.8% weight/volume of a suspending agent,

[0032] wherein said composition and does not contain polysorbate, polyethylene glycol, glycerol or sorbitol.

[0033] In one embodiment of the present invention, the concentration of megestrol acetate in the flocculated suspension is preferably about 10 to 200 mg per ml, more preferably about 20 to 60 mg per ml and most preferably about 40 mg per ml. It is preferred that the megestrol acetate is micronized so that 90% of the weight of particles is below 20 microns and the mass median diameter is between 3.0 and 10 microns.

[0034] The wetting agent (i.e., surfactant) of the present invention can be anionic or non-ionic.

[0035] Suitable anionic wetting agents include, for example, salts of sulphonic or monoesterified sulphuric acids such as alkyl benzene sulphonate, alkyl sulphates, alkyl ether sulphates, olefin sulphonates, alkyl phenol sulphates, alkyl phenol ether sulphates, alkyl ethanolamine sulphate, alkyl ethanolamine ether sulphates, alpha sulpho fatty acids or esters. Other suitable anionic wetting agents include fatty alkyl sulphosuccinates, fatty alkyl ether sulphosuccinates, acyl sarcosinates, acyl taurides, and paraffin sulphonates. The preferred anionic wetting agents are salts of alkali metals or alkaline earth metals, preferably docusate sodium, sodium lauryl sulfate and docusate calcium. Other salts include ammonium, monoethanolamine, diethanolamine, triethanolamine and alkyl amines having up to 7 aliphatic carbon atoms.

[0036] Suitable non-ionic wetting agents include, for example, sorbitan fatty esters, polyoxyethylene stearates, polyoxyethylene alkyl ethers, polyethylene-propylene glycol copolymer (poloxamer), and polyoxyethylene castor oil derivatives. Preferred polyoxyethylene castor oil derivatives include polyoxyl 5 castor oil, polyoxyl 9 castor oil, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 40 hydrogenated castor oil and polyoxyl 60 hydrogenated castor oil.

[0037] Wetting of a non-polar solute such as megestrol acetate takes place because it forms an association complex

through Van der Waals interactions with a hydrophobic moiety of the surfactant (wetting agent). This effectively wets the material because the hydrophobic group of the surfactant is sequestering the megestrol while the hydrophilic group of the surfactant is solubilized in the bulk water.

[0038] In one embodiment of the present invention, the wetting agent of the present invention has a straight carbon chain of up to 20, preferably 4-20, atoms in the hydrophobic group. In another embodiment, the straight carbon chain of the surfactant is less than 10 atoms, such as the one in ducosate.

[0039] The wetting agent of the present invention is present in the composition at a concentration of about 0.04 to 0.4% weight/volume, preferably at a concentration of about 0.04 to 0.1%. Conventional pharmaceutical carriers can be present, e.g., conventional suspending agents, protective colloids, preservatives, buffers, sweeteners/density adjusters and flavoring agents.

[0040] The use of a suspending agent maintains the megestrol acetate particles in a uniformly suspended state for a longer period of time during the dose administration period thereby permitting uniform dosing. Suitable suspending agents include, for example, xanthan gum, acacia gum, carrageenan, carbomer, sodium carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and a mixture of microcrystalline cellulose and carboxymethylcellulose sodium. The suspending agent of the present invention is present in the composition at a concentration of about 1.2 to 1.8% weight/volume, preferably at a concentration of about 1.5 to 1.8%.

[0041] In some instances it may be desirable to use a protective colloid. The protective colloid is adsorbed onto the megestrol acetate particles and increases the strength of the hydration layer formed around suspended particles through hydrogen bonding and molecular interaction. This activity thus "protects" the megestrol acetate particles from binding to other particles and subsequent settling and caking. Suitable protective colloids include, for example, gelatin, acacia, carrageenan, carbomer, sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and xanthan gum. The protective colloid is generally present at a concentration of less than about 0.2% by weight/volume, preferably at a concentration of about 0.13 to 0.18%.

[0042] Suitable preservatives include, for example, sodium benzoate, benzoic acid, butylparaben, methylparaben, ethylparaben, propylparaben, phenylethyl alcohol, EDTA, benzyl alcohol, and phenoxyethanol. A preservative is typically used at a concentration of about 0.1 to 0.3% weight/volume, e.g., 0.15 to 0.25% weight/volume.

[0043] Suitable buffers (pH adjusters) include, for example, citric acid/sodium citrate, hydrochloric acid, succinic acid/sodium succinate, lactic acid, and potassium citrate. The buffer may be used to adjust the pH level of the suspension to a desired pH. In one embodiment, for example, a citric acid/sodium citrate is used where the citric acid level is held constant (e.g., 0.244%) and the pH is adjusted with sodium citrate (e.g., 0.015-0.11%).

[0044] In order to produce a non-flocculated (smooth) suspension, it is necessary that the pH of the suspension should be above a certain level, i.e., at least about 3.3.

Another embodiment of the invention, therefore, is where the composition has a pH of at least about 3.3. By adjusting the pH in this manner, it is possible to obtain a suspension that is non-flocculated. It may be possible, however, that an initially non-flocculated suspension produced in this manner might develop some level of flocculation after being stored for a certain period of time. Of course, the present invention covers both the non-flocculated and flocculated forms, i.e., suspensions having any level of flocculation.

[0045] If the pH of the suspension is too high, however, there is a reduction in the effectiveness of sodium benzoate when used as a preservative in the formulation. Specifically, there is a reduction in the antimicrobial properties of sodium benzoate at high pH levels. Accordingly, if sodium benzoate is used as a preservative, it is preferable to keep the pH of the suspension at about 5.0 or less. Therefore, another embodiment of the present invention is where the composition has a pH of about 3.3 to 5.0, preferably about 3.6 to 4.6.

[0046] Suitable sweetening/density adjusting agents include, for example, sucrose, saccharin sodium, corn syrup and mannitol. A sweetening/density adjusting agent is typically used at a concentration of about 5 to 10% weight/volume, preferably about 5%. Flavoring agents are typically used at a concentration of about 0.35% weight/volume and include, for example, lemon and lemon-lime flavor.

[0047] The composition of the present invention contains less than about 1.0% weight/volume of propylene glycol, preferably less than about 0.5%, most preferably less than about 0.35%. If propylene glycol is present at all in the composition, it is generally present as an ingredient in the flavoring agent.

[0048] As apparent from the above discussion, various combinations of the wetting agents, suspending agents and other additives may be used in the formulation of the present invention, and certain specific ingredients may be added to perform special functions as needed. Although not specifically set forth herein, additional pharmaceutically acceptable carriers, adjuvants and additives may be employed, when necessary, to enhance stability or improve dissolution performance and bioavailability.

[0049] In a preferred embodiment, the wetting agent is polyoxyl 35 castor oil and the suspending agent is a mixture of microcrystalline cellulose and carboxymethylcellulose sodium.

[0050] A more specific embodiment of the oral pharmaceutical composition of the present invention is a stable suspension in water comprising about 40 mg of micronized megestrol acetate, about 0.04 to 0.4% weight/volume of polyoxyl 35 castor oil, about 1.2 to 1.8% weight/volume of a mixture of microcrystalline cellulose and carboxymethylcellulose sodium, about 0.15 to 0.25% weight/volume of sodium benzoate, about 0.24% weight/volume of citric acid, about 0.015 to 0.11% weight/volume of sodium citrate, about 5% weight/volume of sucrose, about 0.35% weight/volume of flavor, and the remainder water, wherein said composition contains less than about 0.35% weight/volume of propylene glycol and does not contain polysorbate, polyethylene glycol, glycerol or sorbitol. This more specific embodiment preferably has a pH of at least about 3.3, most preferably about 3.3 to 5.0.



US005712310A

United States Patent [19]**Koch**[11] **Patent Number:** **5,712,310**[45] **Date of Patent:** **Jan. 27, 1998**[54] **SUSPENSION OF SUBSTANTIALLY WATER-
INSOLUBLE DRUGS AND METHODS OF
THEIR MANUFACTURE**

5,183,829	2/1993	Caldwell	514/570
5,374,659	12/1994	Gowan, Jr.	514/557
5,401,510	3/1995	Robertson et al.	424/427

[75] **Inventor:** **Edward A. Koch**, New Freedom, Pa.[73] **Assignee:** **Alpharma USPD, Inc.**, Baltimore, Md.[21] **Appl. No.:** **664,338**[22] **Filed:** **Jun. 14, 1996**[51] **Int. Cl.⁶** **A61K 9/107; A61K 31/19**[52] **U.S. Cl.** **514/570**[58] **Field of Search** **514/570**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,282,215	8/1981	Dudzinski et al.	514/161
4,404,210	9/1983	Schmidt	514/282
4,569,937	2/1986	Baker et al.	514/282
4,571,400	2/1986	Arnold	514/282
4,587,252	5/1986	Arnold	514/282
4,783,465	11/1988	Sunshine et al.	514/255
4,788,220	11/1988	Mody et al.	514/557
4,857,331	8/1989	Shaw et al.	424/440
4,859,704	8/1989	Haas	514/557

FOREIGN PATENT DOCUMENTS

WO 92/00731 1/1992 WIPO.

OTHER PUBLICATIONSTechnical Bulletin DB-33 *Xanthan Gums For Food and Pharmaceutical Applications*, Kelco a Division of Merck & Co., Inc. 1-3.S.L. Law et al. *Drug Development and Industrial Pharmacy*, 10(7), 1049-1069 (1984).*Primary Examiner*—Alan L. Rotman*Assistant Examiner*—D. Margaret M. Mach*Attorney, Agent, or Firm*—Lerner, David, Littenberg, Krumholz & Mentlik[57] **ABSTRACT**

A stable aqueous suspension including a substantially water-insoluble drug suspended in a completely water-soluble mixture including hydroxypropylmethylcellulose, polyoxy-ethylenc sorbitan monooleate, and xanthan gum.

56 Claims, 1 Drawing Sheet

SUSPENSION OF SUBSTANTIALLY WATER-INSOLUBLE DRUGS AND METHODS OF THEIR MANUFACTURE

FIELD OF THE INVENTION

The present invention relates to the pharmaceutical field and, in particular, to the design of drug suspensions for substantially water-insoluble drugs, such as ibuprofen, and methods of manufacturing same.

BACKGROUND OF THE INVENTION

Few drugs since the introduction of aspirin have had as pronounced an effect on the pharmaceutical industry and the consuming public as ibuprofen. Since the FDA approved the sale of ibuprofen as an over-the-counter drug, its popularity has climbed dramatically. Today, ibuprofen is one of the most recognized and most used drugs for aches, pains, and fevers.

Nonetheless, ibuprofen, like many other substantially water-insoluble drugs, has been unable to fulfill its full potential in the marketplace, particularly in areas where liquid dosage forms are preferred. Children, older persons, and many others, including disabled and incapacitated patients, have trouble swallowing whole tablets or even capsules. Drug suspensions, properly formulated, could find ready acceptance with these very important groups of patients. Not surprisingly, there have been numerous attempts to formulate aqueous pharmaceutical suspensions of substantially water-insoluble pharmaceutical active ingredients, such as, for example, ibuprofen. Many of these formulations, while satisfactory, still leave room for improvement.

For example, numerous drugs have been formulated in solutions and suspensions with alcohol (ethanol). However, such formulations are obviously unsuitable for children, alcoholics and those on certain drugs. Gowan, Jr., U.S. Pat. No. 5,374,659, teaches an aqueous pharmaceutical suspension including a water-insoluble active ingredient such as ibuprofen, in a suspension comprised of xanthan gum, pregelatinized starch, and polyoxyethylene sorbitan monooleate (polysorbate 80), a taste-masking composition, and water. However, while Gowan's formulation excludes ethanol, it is not without its problems.

First, one of Gowan's disclosed ingredients is a corn starch. Corn starch is a known allergen. Thus the Gowan formulation would be contraindicated in those people, particularly children, with a known corn allergy. Furthermore, corn starch supports microbial growth and is subject to microbial degradation. While Gowan does disclose the use of an antimicrobial agent, the starch is added prior to the addition of the antimicrobial agent. Thus there is an increased potential for microbial growth during the manufacturing process. Microbial growth during manufacturing places a greater burden on the antimicrobial agent and could lead to chemical and physical changes in the corn starch itself. This could affect the properties of formulations from batch to batch.

It is therefore desirable to produce a suspension which excludes starch. One possible candidate to replace starch is microcrystalline cellulose. In fact, such a formulation is discussed in Mody et al. U.S. Pat. No. 4,788,220. Though the use of microcrystalline cellulose will overcome some of the disadvantages of corn starch, it is, nonetheless, a water-insoluble material. Therefore, it is not without its own limitations.

As to solubility, insoluble materials such as starch, microcrystalline cellulose or clays such as magnesium aluminum

silicate, which are often used as suspending agents, may mask inhomogeneity in the product. Thus, while a product may look homogeneous, the active ingredient is not evenly distributed throughout the suspension. A consumer might then ignore instructions to shake before using because the product appears visibly homogeneous. Under such circumstances, if the drug was not, in fact, homogeneously dispersed, the patient could potentially receive either a sub-potent or super-potent dose.

Another disadvantage which stems from the use of insoluble materials (other than the drug substance) in a drug product suspension is that the drug substance particle size in the dosage form is more difficult to evaluate. The drug particle size in a suspension can affect the bioavailability and the physical stability of the dosage form. Thus monitoring the drug particle size, both at the time of manufacture and during shelf storage, is an important parameter from both a quality and regulatory standpoint. One of the most common techniques is the use of a laser light scattering instrument such as manufactured by Malvern or Coulter. These instruments are able to take a large number of replicate readings in a short period of time with a relatively large sample size as compared to the alternate manual sizing using a microscope. However, laser light scattering instruments cannot differentiate between the insoluble drug particles and the insoluble suspending agents making all such measurements imprecise. The alternative to laser light scattering would be direct manual microscopic particle sizing. This technique is costly in terms of the analysis time and it is more subjective, thus less precise. Other formulations have also been proposed such as those described in Caldwell, U.S. Pat. No. 5,183,829.

SUMMARY OF THE INVENTION

The inventor has created a new, water-soluble, suspension vehicle which is useful for the administration of generally water-insoluble drugs such as ibuprofen and which overcomes the shortcomings identified in the prior art. In a preferred aspect, the present invention provides a storage stable, aqueous suspension for delivery of at least one substantially water-insoluble pharmaceutically active agent. The suspension includes at least one substantially water-insoluble pharmaceutically active agent provided in an amount which is effective to treat a patient in need of such treatment. The substantially water-insoluble pharmaceutically active agent is suspended in a formulation which includes a first suspending agent which is a pharmaceutically acceptable, non-ionic, water-soluble, modified cellulose. The formulation also includes a second suspending agent which is a water-soluble, hydrocolloidal polysaccharide. The suspension also includes a non-ionic, water-soluble wetting-agent. The first suspending agent, the second suspending agent and the wetting-agent are provided in amounts which are effective to form a stable suspension of the water-insoluble pharmaceutically active agent.

In a particularly preferred aspect of the present invention, the substantially water-insoluble pharmaceutically active agent is selected from a group consisting of cardiovascular drugs, hypoglycemic drugs, sedatives/hypnotics, antiepileptics, psychopharmacologic agents, analgesics, antipyretics, anti-inflammatory agents, anti-neoplastics and antimicrobials. Most preferably, the modified cellulose is hydroxypropyl methylcellulose. The second suspending agent preferably has a shear thinning profile similar to that of xanthan gum. That is to say that the second suspending agent is capable of imparting, in combination with these formulations, a suspension exhibiting at least a 100%

increase in viscosity for each log decrease of shear rate in the range of 20 sec^{-1} to 0.2 sec^{-1} . Most preferably, the second suspending agent is xanthan gum. The wetting-agent is preferably polysorbate 80.

It is advantageous for the suspensions of the present invention to also include at least one additional material selected from a group consisting of a sweetener, a humectant, a viscosity modifier, an antimicrobial agent, a pH modifier, a flavoring and/or a coloring.

In another preferred aspect of the present invention, there is provided a storage stable, aqueous suspension for delivery of at least one substantially water-insoluble pharmaceutically active agent. The suspension includes at least one substantially water-insoluble pharmaceutically active agent selected from a group consisting of: analgesics, antipyretics, and anti-inflammatory agents. The substantially water-insoluble pharmaceutically active agent can be present in an amount of between about 0.1% and about 20% w/v. The pharmaceutically active agent is suspended in a formulation including a first suspending agent which is a pharmaceutically acceptable, non-ionic, water-soluble, modified cellulose provided in an amount of between about 0.4% and about 1% w/v, a second suspending agent which is a water-soluble, hydrocolloidal polysaccharide being provided in amount of between about 0.1% and about 1.0% w/v and a water-soluble, non-ionic wetting-agent provided in an amount of between about 0.025% and about 0.4% w/v.

Most preferably, the present invention provides a stabilized suspension comprising ibuprofen in amounts between about 0.5% and about 8 w/v, hydroxypropyl methylcellulose in an amount of between about 0.4% and about 1% w/v, xanthan gum provided in an amount of between about 0.1% and about 1.0% w/v, polyoxyethylene sorbitan monooleate in an amount of between about 0.025% and about 0.4% w/v, sucrose in an amount of between about 20% and about 40% w/v, glycerin in an amount of between about 1% and about 40% w/v, an antimicrobial agent in an amount of between about 0.05% and about 0.5% w/v; a pH modifier in an amount of between about 0.05% and about 1.0% w/v, at least one flavoring and water.

Stated another way, in one aspect of the present inventions there is provided a suspension which is composed exclusively of generally water-soluble ingredients, other than the pharmaceutically active agent. That suspension is stable, non-reactive, cost effective, and overcomes many of the disadvantages that are inherent in suspensions created using substantially water insoluble ingredients. The aqueous suspension formulations of the present invention could be used in many contexts. But they are particularly useful as drug delivery vehicles. In fact, it has been found that the suspensions of the present invention, made of generally water soluble components, are an excellent means for suspending otherwise substantially water-insoluble pharmaceutically active agents or drugs.

Suspensions of substantially water-insoluble drugs suspended in the formulations of the present invention have several advantages over the prior art. First, because the present invention eliminates corn starch, the resulting dosage form can be administered to patients with corn starch allergies. Further, the elimination of starch from the formulation reduces the risk of bacterial growth during processing as well as the viability in the formulation that may result. Moreover, because the present invention does not generally use substantially water-insoluble materials, other than the drug, better process control is possible. The potential for masking of an inhomogeneous dispersion of the drug is also eliminated.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. illustrates the relationship between viscosity and shear rate for solutions containing KELTROL T brand Xanthan Gum available from Kelco, a division of Merck & Co., Inc., over a shear rate range between 0.01 and 10,000 1/sec as measured on the Rheometrics Fluids Rheometer.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A suspension in accordance with the present invention must satisfy several criteria. First, it must be a suspension as opposed to a slurry, emulsion, solution or gel. A pharmaceutical suspension can generally be defined as a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. The particles have diameters, for the most part, greater than about 0.1 micrometers, and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity. Suspensions can be flocculated or structured. Structured suspensions are preferred, however, some flocculation in a structured suspension is possible under certain conditions. In addition, the suspensions must be stable, both in terms of the nonreactivity of the various components and in terms of long term storage stability. A "stable" suspension in accordance with the present invention is one which can be redispersed homogeneously with moderate shaking and can be poured easily throughout its shelf life, with neither the particle size distribution, the form or the physiological availability of the suspended active agent changing appreciably with time. The stability of a suspension is often judged by criteria set in the U.S.P. listed under the heading "Stability Considerations in Dispensing Practice." These criteria require, inter alia, that the original physical properties, including appearance, palatability, uniformity, dissolution and suspendability of the suspension be retained. Most preferably, a suspension in accordance with the present invention will have a viscosity profile which will vary with the conditions applied to the suspension. For example, preferably, a bottle containing a suspension of the present invention will exhibit a generally low viscosity when the bottle is shaken or when the bottle is manipulated during pouring. However, when the suspension is sedentary, its relative viscosity will increase to assist in maintaining the integrity of the suspension and the homogeneous distribution of the active ingredient(s).

The suspension should also be cost-effective to manufacture and should reduce the concerns any patient may have with regards to adverse reactions to its ingredients. Finally, in accordance with the present invention, the suspension should be a substantially aqueous dosage form which can be effectively used for the administration of water-insoluble or sparingly water-soluble drugs.

For the purposes of the present invention, the terms "substantially water-insoluble" and "insoluble" refer generally to compositions which are insoluble, practically insoluble or only slightly soluble in water as those terms were defined in the U.S.P., Remington: "Pharmaceutical Science", 18th edition published by Mack Publishing Company and as used in the industry. Substantially water-insoluble pharmaceutically active ingredients include, for example, cardiovascular drugs, e.g. cardiac glycosides, clofibrate and probucol; hypoglycemic drugs; sedatives/hypnotics, e.g. barbiturates; and antiepileptics, e.g. carbamazepine, mephenytoin and phenytoin; psychopharmacologic agents e.g. perphenazine, analgesic antipyretic and anti-inflammatory agents, e.g. naproxen, oxycodone and indomethacin; anti-neoplastic drugs such as almitrine; and

antimicrobials such as erythromycin estolate. In accordance with the present invention, particularly preferred classes of insoluble drugs include: analgesics, antipyretics, anti-inflammatory agent, antimicrobials, decongestants and antihistamines. Ibuprofen suspensions are particularly preferred in accordance with the present invention.

In general, aqueous pharmaceutical suspensions in accordance with the present invention will include an amount of at least one water-insoluble, pharmaceutically active agent which is sufficient to treat a patient in need of treatment with that active drug. Of course, the amount of active agent used will vary with the size, sex, age, general health and condition of the patient and the type of drug and suspension. However, generally, from about 0.1% to about 20% weight to volume ("w/v") of at least one substantial water-insoluble pharmaceutical active agent is used. Of course, it is possible, depending on the nature of the dosage form, the drug(s), and the indication(s), to create suspensions in accordance with the present invention that have greater than about 20% and/or less than about 0.5% of at least one insoluble active ingredient.

More preferably, however, on a weight to volume basis, the amount of the substantially water-insoluble pharmaceutically active agent included in the suspensions of the present invention ranges from between 0.5% to about 10%. In terms of ibuprofen, the suspension preferably contains between 0.5% to about 8% ibuprofen w/v. More preferably, the suspensions in accordance with the present invention contain between 1% and about 4% active (such as ibuprofen) and most preferably about 2% w/v. The particles should have a median diameter of at least about 0.1 micrometers. The maximum particle size is not critical so long as the particles are capable of being maintained in a stable suspension. However, particle sizes of up to about 100 microns (median diameter) and preferably up to about 50 microns are useful in accordance with the present invention. Particles in a size range of between about 15 and about 35 microns are particularly preferred.

The suspensions in accordance with the present invention are principally achieved by combining the drug with three ingredients including a first water-soluble suspending agent, a second water-soluble suspending agent and a water-soluble surfactant. The balance, of course, is water.

In accordance with the present invention, the first water-soluble suspending agent can be any pharmaceutically acceptable, non-ionic, water-soluble, modified cellulose. Particularly preferred modified cellulose compounds include hydroxypropyl cellulose ("HPC"), methyl cellulose ("MC"), hydroxyethylcellulose ("HEC") and hydroxypropyl methylcellulose ("HPMC").

It has been found that such water-soluble suspending agents may be used in place of such compounds as starch and microcrystalline cellulose, thereby overcoming the problems associated with insoluble suspending agents. In view of the arts' use of insoluble suspending agents, it was surprising to learn that using water-soluble suspending agents produced suspensions of equal or greater performance. It was even more surprising to find that only certain types of water-soluble suspending agents would work as the first suspending agent. Other conventional water-soluble suspending agents, such as, for example, guar gum, were found by the inventor to be inadequate first suspending agents. The use of the first water-soluble suspending agent described in accordance with the present invention eliminates the problems associated with the use of water-insoluble suspending agents, and in addition, eliminates one

potential source of an allergic response and microbial growth from the formulation.

It has also been discovered that in addition to the general advantages which inure from the use of certain water-soluble suspending agents as described herein, certain specific water-soluble suspending agents, such as HPMC, provide unexpected and superior results. For example, it was previously reported by Law and Kayes, "The Stability Of Suspensions In The Presence Of Non-Ionic Water-soluble Cellulose Polymers," *Drug Development and Industrial Pharmacy*, 10(7), 1049-1069 (1984), that an ibuprofen suspension could be made using HPMC. The authors reported that at low levels of HPMC, (0.04%) a re-dispersible dispersion of flocs could be formed. However, as the concentration of HPMC exceeded 0.04%, caking resulted which led to high redispersibility values (meaning it was difficult to form a homogeneous suspension). The authors went on to state that at higher polymer levels, a gel structure could result which would lead to increased difficulty in obtaining a homogeneous dispersion. In fact, the Law and Kayes article specifically speaks of forming a flocculated suspension using low level (0.04% and lower) of HPMC. When levels were increased to 0.08%, the suspensions were deflocculated and formed a cake which was difficult to re-disperse.

It has been found, however, that using the system of the present invention, it is possible to use HPMC at levels which are as much as 1000% higher than that suggested by Laws and Kayes, while at the same time, obtaining stable suspensions which are neither visibly flocculated nor caked. In accordance with the present invention, flocculation occurs at around 0.3% HPMC. By increasing the concentration of HPMC to at least about 0.4% and more preferably at about 0.6%, visible flocculation was eliminated and a structured suspension was produced which showed neither separation nor caking. Of course, the occurrence of floc in a suspension is less desirable than a fully structured, homogeneous suspension. However, as flocs can be readily re-dispersed within a suspension upon shaking, it is far more desirable to obtain flocculation than to obtain a non-redispersable cake. For that reason, the first water-soluble suspending agent can be used in an amount of as little as about 0.2%. However, preferably between about 0.4% and about 1% and more preferably between about 0.5% and about 0.7% w/v of HPMC is used. Most preferably, HPMC is provided as a first suspending agent in an amount of about 0.6% w/v. The preferred ranges also apply generally to any first water-soluble suspending agent used in accordance herewith. HPMC is Available from Dow Chemical Co., Midland Mich. 48674.

The second principal ingredient of the suspension is the second water-soluble suspending agent. This second suspending agent is intended to provide the suspension with a specific viscosity profile. Generally, the second suspending agent is a water-soluble hydrocolloidal polysaccharide such as guar gum, carrageenan gum, gum arabic and xanthan gum. Certain materials, such as for example, xanthan gum have known viscosity profiles which vary responsive to an applied shear. This is also referred to as a "shear thinning profile." For example, KELTROL T, a xanthan gum available from Kelco, a division of Merck & Co., Inc. 75 Terminal Ave. Clark, N.J. 07066, exhibits an increase in apparent viscosity with a decrease in applied shear. The viscosity or shear thinning profile for xanthan gum and other similar compounds are well known and well documented. See FIG. 1. Any material which can provide a similar shear thinning profile to xanthan gum could be used for in accor-

dance with the present invention. Stated another way, compounds useful as the second suspending agent in accordance with the present invention will have a shear thinning profile whereby a suspension exhibiting at least a 100% increase in viscosity for each log decrease of shear rate in the range of 20 sec^{-1} to 0.2 sec^{-1} results. In fact, for a log decrease in shear from 20 sec^{-1} to 2.0 sec^{-1} , the viscosity of the suspension should double. From 2.0 sec^{-1} to 0.2 sec^{-1} , the viscosity of the suspension should about double again.

It should be noted that while such compounds as guar gum are unacceptable as the first suspending agent in accordance with the present invention, they are acceptable for use as the second suspending agent. The fact that the first and second suspending agents are not interchangeable is not important or surprising. What is important is that the two distinct suspending agents have two distinct functions in these formulations.

The second suspending agent must be included in an amount which is effective to provide the resulting suspension with the desired shear thinning profile. Generally, the amount of the second suspending agent used will vary depending upon the nature and quantity of the other ingredients as well as the second suspending agent selected. However, a range of between about 0.1% and about 1.0% w/v is generally useful. A more preferred range for the second suspending agent in accordance with the present invention is from between about 0.1% and about 0.3% w/v. Even more preferably, the amount of the second suspending agent used will range from between about 0.15% and about 0.21%. Xanthan gum is the preferred second suspending agent in accordance with the present invention, and when used, it is preferably used in an amount of about 0.18% w/v.

The non-ionic, water-soluble wetting-agent is the third necessary component. Such wetting-agents or surfactants are well known in the art and include, for example, polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monooleate also known as polysorbate 80. Other useful wetting-agents in accordance with the present invention include polyoxyethylene-polyoxypropylene copolymers which are poloxamers. Poloxamers such as poloxamer 124, 188, 237, 388 and 407 available from BASF Corp. of Parsippany, N.J. 07054 may also be used. Polyvinyl alcohol available from Spectrum Chemical Mfg. Corp., New Brunswick, N.J. 08901 may also be used as well.

The wetting-agent is generally provided in an amount of between 0.025% to about 0.4%, more preferably in the amount of 0.05% to about 0.2% and most preferably in amounts of about 0.1% weight to volume. The preferred wetting-agent in accordance with the present invention is polysorbate 80.

Water and preferably distilled, deionized water is the last necessary ingredient. Water is added as needed to dissolve the various components and to bring the suspensions to correct volume.

In addition to the principal ingredients just described, suspensions in accordance with the present invention also desirably contain a number of secondary ingredients including, without limitation, sweeteners, humectants, viscosity modifiers, antimicrobial agents, and pH modifiers. These ingredients may be included to the extent that they do not alter the basic and novel characteristics of the invention. Thus, these additives should be selected such that they will not unduly undermine the stability or other advantageous properties of the suspension. It has been found that certain secondary ingredients can actually enhance the stability, the viscosity and/or the organoleptic properties of these formu-

lations. Obviously, the selection of such sweeteners, humectants, viscosity modifiers, antimicrobial agents and pH modifiers is preferred.

Without wishing to be bound by any particular theory of operation, sweeteners such as sucrose and humectants such as glycerin, at the concentrations used, contribute directly to the viscosity, stability and/or organoleptic properties of the suspension in that they are at least slightly more viscous than water. Second, these compounds also exhibit a direct effect on the formulations by reducing the total water quantity available, thereby increasing the effective concentrations of the suspending agents and wetting-agents. The other secondary ingredients will also have an effect on the viscosity, stability and organoleptic properties of the suspensions of the present invention. Antimicrobial agents such as, for example, sodium benzoate, and pH modifiers, such as citric acid, effect the ionic strength and the pH of the suspensions. Therefore, while only certain compounds will be discussed herein, it is understood that any functionally similar ingredient(s) could be used in their place.

Sweeteners in accordance with the present invention directly enhance the organoleptic properties of the suspensions and act as, inter alia, taste masking agents. As previously discussed, they also play a role in the viscosity and stability of the formulations. The preferred sweetener in accordance with the present invention is sucrose and, more preferably sucrose syrup #2 (67.4% w/w solution of sucrose in water) is used. Other acceptable sweeteners include, without limitation, sugars such as fructose and glucose and sweet polyhydric alcohols which are commonly used as sweeteners such as sorbitol, mannitol or xylitol. These sweeteners are all sweet, relatively non-ionic, and substantially water-soluble. The amount of sweetener used in accordance with the present invention can vary based on a number of factors. Of course, as the sweetener may have an effect on the viscosity of the suspension, sufficient sweetener must be provided so as to assist in providing the desired viscosity. Because the sweetener also plays a large role in taste masking, if the active agent is particularly bad tasting then more sweetener may be needed. Generally, the amount of sweetener ranges from between about 20% and about 40% w/v. However, preferably, the amount used should range between about 25% and about 35% w/v.

Another ingredient which should be used in the suspension of the present invention, particularly those which use a sugar as the sweetener, is a humectant. A humectant in accordance with the present invention preserves moisture, particularly around the threaded mouth of the bottle and the cap, to ensure that the sugar contained within the formulation does not crystallize, rendering it difficult to open the bottle. A particularly useful compound in accordance with this aspect of the invention is glycerin. Glycerin acts not only as a humectant, but, as previously discussed, also acts as a viscosity modifier in that it ties up water and has a viscosity that is greater than that of water. Moreover, glycerin is substantially non-ionic and water-soluble. It is also a sweetener and has antimicrobial efficacy. Other pharmaceutically acceptable humectants include, without limitation, propylene glycol and sorbitol. These humectants, as well as other known compounds, may also be used solely as viscosity modifiers for the suspensions of the present invention. For example, if sorbitol is used as the sweetener, then there is no reason to use a humectant. However, it may be desirable to add a viscosity modifier such as propylene glycol or glycerin to the sorbitol in an amount which is necessary to bring the viscosity of the suspension up to the desired level. The amount of the viscosity modifier/

humectant used can vary widely. However, a combined total of these compounds should generally range from between about 1% and about 40%, and more preferably between about 1% and about 15% w/v.

It should be noted that, although glycerin is sweet, it generally cannot be used as a complete substitute for sweeteners such as sucrose. First, glycerin does not have the sweetening power of sucrose. Thus a relatively high glycerin content would be needed. Moreover, glycerin, like propylene glycol, acts as a solvent which is a negative factor in accordance herewith. As more drug is solubilized, the potential for Ostwald ripening increases thus increasing the potential for a change in the distribution of the drug from unimodal to multimodal. Changes in the size distribution of the drug particles, sedimentation rates and or changes in bioavailability may also result. Thus the selection and use of compounds in this system may often require a balance of factors.

Antimicrobial agents, such as sodium benzoate, potassium sorbate and sodium propionate, to name but a few should also be used. These antimicrobial agents are well known in the industry. The antimicrobial agents used should not interfere with the suspension, must be water-soluble, and must not adversely affect the taste or the pH of the mixture. The amounts of such antimicrobial agents can vary widely. For example, the amount of sodium benzoate which may be used at a range of between about 0.05% and about 0.5% w/v. Preferably, the amount of antimicrobial agent used may range from between about 0.1% and about 0.5% w/v. However, the addition of, for example, too much sodium benzoate, may elevate the pH to a degree which will require the addition of an undesirable excess of a pH modifier.

The pH modifiers used in accordance with the present invention may be any food grade or pharmaceutical grade acid or base which is capable of maintaining the pH of the resulting formulation in a range of between about 2.5 and about 5.0. Preferably, the pH of the formulation is between about 3.6 and about 4.6. Citric acid is a preferred acidifying agent. Generally, the citric acid is provided in an amount of between about 0.05% and about 1.0% w/v. Any combination of antimicrobial agents and pH modifiers with yield a generally equivalent ionic strength and pH, and which are pharmaceutically acceptable, are contemplated.

Furthermore, to achieve the desired levels of ionic strength and pH, a weak acid and a salt of a weak acid can be used. For example, the functions of an antimicrobial agent and a pH modifier can be obtained by the use of, for example a mixture of benzoic acid and sodium citrate.

While not in any way important to the formation of a stable suspension in accordance with the present invention, nonetheless, an acceptable combination of colorants, additional sweeteners and flavors are necessary to ensure that the resulting suspension has desirable organoleptic properties. Any conventional excipients can be used so long as they do not adversely affect the suspension and are water-soluble. Flavors can include vanilla, strawberry, cherry, mixed berry, raspberry, blackberry, banana, apple, pear, peach, grape, pineapple, mint, wintergreen, peppermint, spearmint, cinnamon, spice, chocolate, hazelnut, coffee and the like. Dyes acceptable for orally ingested products which are detailed in the Code of Federal Regulations may also be used.

The resulting suspensions preferably have a viscosity of about 100 centipoise when measured at a temperature of about 25° C. and at a shear rate of 20 sec⁻¹. As previously mentioned, the viscosity should at least about double for

each log decrease in the shear rate. There is no real upper limit to the viscosity of the suspensions so long as they remain free flowing and pourable liquids. However, after shaking, the suspension should be easily dispensed by the consumer.

Thus the suspensions of the invention can be considered as consisting essentially of a first water-soluble suspending agent, a second water-soluble suspending agent having a specific viscosity profile, a water-soluble wetting-agent and water. Other ingredients can also be added so long as they do not detract from the advantageous properties of the suspensions of the present invention. These may include, without limitation, sweeteners, humectants, viscosity modifiers, antimicrobial agents and pH modifiers, as well as flavorings, coloring and other conventional excipients. Ingredients which actually enhance the properties of the suspensions, such as sucrose, glycerin, sodium benzoate and citric acid, and their functional equivalents, are specifically contemplated hereby.

In particularly preferred aspects of the present invention, the suspensions are formulated without the use of generally water-insoluble compounds or components. Of course, relatively small amounts of such compounds, or insoluble compounds that may be very small in terms of particle size, may be used, so long as they neither compromise the utility of the suspension nor significantly detract from the advantages which result from the use of water soluble ingredients.

The suspensions of the invention can generally be made by any conventional process. This includes the use of the sequential addition of various components to a main phase. Specifically, a slurry is created by the addition of hot (80°-85° C.) purified water USP (deionized water) and the HPMC in a mixing vessel. The HPMC is mixed in the hot water until a uniform slurry is produced. Thereafter, cold water is added to the mixing vessel. The cold water should be about room temperature or below. Agitation continues during this second water addition such that a uniform slurry is maintained. Thereafter, the resulting mixture is force cooled to below 25° C. This can be accomplished by, for example, using a jacketed vessel with suitable coolant. It is possible to refrigerate the main phase created hereby to any temperature above freezing. However, a temperature of greater than 5° C. and below about 25° C. is preferred.

In a separate vessel, a small portion (approximately 10%) of glycerin USP (96%) is charged and the xanthan gum is then dispersed therein. This is accomplished again using constant mixing. The remaining 90% or so of the glycerin is added to the force-cooled main phase, also with constant mixing, such that a homogeneous solution is formed. Upon completion of the dispersion of the glycerin and xanthan gum, mixing is stopped and the resulting slurry is immediately added to the main phase. Mixing of the main phase continues.

A further quantity of purified water at a temperature of between 50° to about 55° C. is then transferred to a separate mixing container and the surfactant is added thereto. The antimicrobial agent is then dissolved in the solution, again with constant mixing. The resulting solution of antimicrobial agent, surfactant and water is then added to the main phase while mixing continues.

After the addition of the wetting-agent-containing solution, an acidifying agent is used to adjust the pH of the main phase, where necessary, to between about 2.5 to about 5 and more preferably from between a pH of 3.6 and about 4.6. A sweetener is then added and dissolved in the main phase while mixing. Thereafter, the insoluble drug is then dispersed into the main phase while mixing.

Warm water (40°–45° C.) is then charged to a separate mixing vessel to which is added the necessary coloring agents. Generally, enough warm purified water is added so as to completely dissolve all of the coloring agents used. Thereafter, the dye solution is added the main phase while mixing continues. Finally, a solution is produced of the flavoring ingredient(s). The flavor solution is then added to the main phase while mixing continues.

After all the ingredients have been added to the formulation, the batch weight is then adjusted with purified water to arrive to the theoretical final weight. Preferably, the batch is then passed through a colloid mill. Finally the batch will be deaerated.

EXAMPLES

Example 1

Two formulations in accordance with the present invention were prepared as follows:

TABLE A

Ingredient	Formula A Amount	Formula B Amount
HPMC	6.00 g	7.80 g
Glycerin USP (96%)	80 ml	80 ml
Xanthan Gum, NF	1.80 g	2.34 g
Polysorbate 80, NF	1 g	1 g
Sodium Benzoate, NF	2 g	2 g
Citric Acid, USP anhydrous	2 g	2 g
Sucrose Syrup #2	333 ml	333 ml
Ibuprofen USP	20 g	20 g
FD&C Red #40	0.0100 g	0.0100 g
D&C Yellow #10	0.0250 g	0.0250 g
Flavors	0.6 g	0.6 g
Deionized Water Q.S.A.D. (balance)	1000 ml	1000 ml

*All materials recited in quantity (weight to volume) per liter.

200 ml hot (80°–85° C.) deionized water was added to a suitable beaker. The HPMC was next added to the deionized water and mixed for 15 minutes using a lighting mixer. Next, 347 ml of ambient temperature (room temperature—approximately 25° C.) deionized water was added to the mixture while mixing was continued. The mixture was then cooled to a temperature below 25° C. while mixing continued. This now constitutes the main phase.

10 ml of glycerin was charged to a separate container and the xanthan gum was added thereto. At the same time, the remaining glycerin was added to the main phase and mixed. The mixed xanthan gum/glycerin slurry was then added to the main phase and mixed for 1½ hours.

In a separate beaker, 9.5 ml of water at a temperature of about 45° C. and about 50° C. was charged. The polysorbate 80 and sodium benzoate were then added to the warm water and mixed for 15 minutes using a magnetic stirrer at moderate speed. The mixture was then added to the main phase while mixing continued. Then, the citric acid was added to the main phase while mixing continued for approximately 10 minutes at the same speed.

The sucrose syrup was next added to the main phase. After the addition thereof, the speed of the mixer was increased for a period of 20 minutes. Next, the ibuprofen was added to the main phase. The main phase was then mixed for 3 hours.

In a separate container, 1 ml of deionized water at a temperature of between 35° C. and about 45° C. was added and the red and yellow dyes were added thereto. This

mixture was mixed for 10 minutes by magnetic stirrer and then added to the main phase. A solution was made of the flavors as well. This solution was then added to the main phase and mixing continued for 20 additional minutes. Finally, the batch was adjusted to a theoretical yield by the addition of deionized water and mixing continued for 20 minutes. Formula A was milled and deaerated. Formula B was not deaerated. In each instance, mixing was sufficient to insure a good agitation of the batch without incorporating air.

The resulting materials were stable, opaque orange in color, and judged acceptable in terms of homogeneity, viscosity profile and organoleptic qualities. Furthermore, using standard validated analytical procedures, the resulting formulations showed acceptable storage stability for greater than three months.

Example 2

A suspension was produced as described in Example 1 except that the first suspending agent used was 0.6% w/v of methylcellulose was used in place of HPMC. Processing was identical except that the batch was force cooled to below 8° C. The lower temperature was necessary to fully hydrate the methylcellulose.

The resulting material was stable, opaque orange in color, and judged acceptable in terms of homogeneity, viscosity profile and organoleptic qualities.

Example 3

A suspension was produced as described in Example 1 except that the first suspending agent used was 0.6% w/v of HEC was used in place of HPMC. Further, since the HEC does not need to be hydrated in the same fashion as HPMC, the beginning of the protocol was slightly changed. The HEC was dissolved in warm (50°–55° C.) deionized water. There was no need to force cool the HEC as it hydrates in warm water. From this point on, the protocols are identical, but the temperature of the batch was slightly higher since force cooling was not necessary.

Example 4

A suspension was produced as generally described in Example 1 except that the first suspending agent used was 0.5% w/v of gum arabic (5.00 g/1 L) was used in place of HPMC and the level of Xanthan gum was increased to 0.2% w/v (2.00 g/1 L). The general protocol described in Example 1 was also modified as follows. First, the xanthan gum was dispersed in all of the glycerin. This dispersion was then added to 400 ml of Deionized water and mixed for 30 minutes to form the main phase. Second, the gum arabic was added to 160 ml of boiling deionized water and mixed for 30 minutes. This was then added to the main phase and mixed for 1 hour. Third, sodium benzoate and citric acid were added directly to the main phase and mixed therewith for 15 minutes. Fourth, the Polysorbate 80 was dissolved in 10 ml of warm (55° C.) deionized water and then added to the main phase. The mixing container was rinsed with 10 ml of deionized water and the rinse was added to the main phase. The main phase was then mixed for 15 minutes. Fifth, the ibuprofen was added to the main phase and mixed for three hours. Next the colors and flavors were added as described in Example 1. The sucrose syrup #2 was added and the main phase mixed for an additional 30 minutes. The volume was then adjusted to 1 liter with deionized water, passed through a mill and then deaerated. The resulting material separated within one week and was deemed to be unacceptable. This

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

Abogado
JIMENA ESCOBAR URIBE

ASUNTO	Radicación	05091231
	Trámite	011
	Evento	379
	Actuación	411
	Oficio	10923
	Folios	016

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/EP2004/002528

Fecha de Presentación Internal. Marzo/11/2004.

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 7 a 17 (como se radicó inicialmente)

1.2. Reivindicaciones: Folios: 18 a 21 (como se radicó inicialmente)

1.3. Prioridad: Marzo/12/2003, US, 60/454,145

2. Objeto de la invención

Título de la solicitud: COMPOSICIÓN FARMACEUTICA COMPRENDIENDO ACIDO 5-METIL-2-(2'-CLORO-6'-FLUOROANILINO) FENILACETICO.

El objeto de la presente solicitud de patente de invención consiste en:

Reivindicaciones 1-13: Composiciones líquidas orales que contienen ácido 5-metil-2-(2'-cloro-6'-fluoroanilino) fenilacético.

Reivindicaciones 14-20: Método de preparación de las composiciones o formulaciones.

Reivindicación 21: Método de tratamiento.

El problema planteado en esta solicitud es la necesidad de obtener formulaciones líquidas estables (suspensiones) que contienen ácido 5-metil-2-(2'-cloro-6'-fluoroanilino) fenilacético.

Para solucionar este problema técnico la solicitud en estudio proporciona una formulación líquida de dosificación oral (suspensión) que comprende: agua, ácido 5-metil-2-(2'-cloro-6'-fluoroanilino) fenilacético y un agente de suspensión, obtenidas por un procedimiento en cuyas etapas no está en contacto el medicamento con el amortiguador.

Clasificación Internacional de Patentes (IPC.): A61K31/195, A61K9/00; A61K9/08; A61K9/00; A61K9/08; A61K31/185.

3. De la solicitud de Patente (según el caso)

3.1. Descripción (artículo 28 D. 486)

En la descripción se menciona que una suspensión no se puede lograr, cuando se mezcla componentes tipo amortiguadores con la sustancia activa, antes de adicionar el agente de suspensión, el cual es una mezcla de celulosa microcristalina y carboximetilcelulosa de sodio (folio 11, pg 5). Se allegan ejemplos de formulaciones (suspensiones) con el principio activo ácido 5-metil-2-(2'-cloro-6'-fluoroanilino) fenilacético; pero esto no muestra la ventaja de la composición preparada a través del procedimiento de fabricación reivindicado (reivindicación 14) con respecto a lo mencionado anteriormente (folio 11, pg 5).

3.2. Reivindicaciones (artículo 30 D 486)

A través de todo el capítulo reivindicatorio se utiliza el término aproximadamente, el cual no es conciso.

Las reivindicaciones 7 y 22 no son claras por cuanto son dependientes de ellas mismas.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)).

La reivindicación 21 no es patentable porque se refiere aun método de tratamiento.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: Marzo/12/2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US2002/0028794	Pharmaceutical composition	Mayo/23/2002
D2	US5712310	Suspensión of substantially water-insoluble drugs and methods of their manufacture.	Enero/27/1998

D1 US2002/0028794 (folios : 71-74) D2 US5712310 (folios : 75-81)

6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

6.1 Nivel inventivo (artículo 18 D486)

La reivindicación 1 y sus dependientes 2-13, se refieren a suspensiones estables que incluyen el principio activo ácido 5-metil-2-(2'- cloro-6'-fluoroanilino) fenilacético.

Solicitud

Reivindicación 1 y sus dependientes (2-13)

Una formulación en forma de suspensión utilizada que contiene:	D1 Suspensiones estables utilizadas como antiinflamatorias	D2 Suspensiones estables utilizadas como antiinflamatorias
a) Una sustancia sólida poco soluble en un medio acuoso 5 metil-2-(2'- cloro-6'-fluoroanilino) fenilacético 1.5%	a) Una sustancia sólida poco soluble en un medio acuoso 5-metil 2-(2'- cloro-6'-fluoroanilino) fenilacético	Ibuprofeno, poco soluble, 0.1-20% (folio 76, colum 1 , renglones 5-10)
b) agua		Agua, tabla A (folio 81, colum 11, renglón 34)
c) Un agente de suspensión ejemplo: CMC, CMC sódica, goma xantan.		Hydroxypropyl mehtylcellulose (folio 76, colum 2, renglón 63)
d) Un agente humectante por ejemplo:polisorbato 80,poloxámero188,		Glicerina, tabla A(folio 81, colum 11, renglón 26)
e) sistema amortiguador o modificadores de pH, por ejemplo: ácido cítrico		Acido cítrico (folio 79, colum 8, renglones 16-17); tabla A (folio 81, colum 11, renglón 29)
f) antiespumante (surfactante) simeticona		Surfactante (folio 78, colum 5, renglones 42-43)
g) conservante por ejemplo butilparabeno, etilparabeno, ácido benzoico		Acido benzoico tabla A (folio 81, colum 11, renglón 28)

El documento del Estado de la Técnica más próximo es D1, el cual menciona composiciones farmacéuticas tales como suspensiones acuosas u oleosas, que contienen el principio activo ácido 5-metil-2-(2'- cloro-6'-fluoroanilino) fenilacético (folio:73, pg 2); las formulaciones citadas en D1 (suspensiones) pueden ser preparadas por métodos conocidos en el estado de la técnica (folio: 74, pg 3).

La diferencia entre la solicitud y D1 es que esta solicitud muestra ejemplos de formulaciones correspondientes a suspensiones. En D1 no se menciona que las suspensiones presentaran problemas de estabilidad.

D2 divulgaba previamente, suspensiones para administración oral, estables al almacenamiento, que contienen un principio activo poco soluble como el ibuprofeno (antiinflamatorios) (folio: 76 columna 2, renglones 35-45).

El problema técnico planteado en esta solicitud: que es obtener formulaciones líquidas estables (suspensiones) que contienen ácido 5-metil-2-(2'-cloro-6'-fluoroanilino) fenilacético, se había resuelto previamente mediante el mismo tipo de composiciones farmacéuticas (suspensiones estables) ya conocidas, enseñadas por **D1**.

En la descripción no se presenta evidencia de la solución de un problema de estabilidad, que muestre claramente el problema y la solución, ya que no se presentan los parámetros y datos obtenidos para evaluar la estabilidad supuestamente lograda con las formulaciones reivindicadas, obtenidas por un procedimiento en cuyas etapas no esta en contacto el medicamento con el amortiguador.

Como no existe tal evidencia, un experto podría guiarse por las enseñanzas de **D2** y **D1** para obtener el tipo de suspensiones reivindicadas, cambiando el Aines (antiinflamatorio) en **D2** por el de **D1**, para lograr una formulación como la reivindicada. Por lo cual las reivindicaciones 1-13, no tienen Nivel Inventivo

La reivindicación 14 y sus dependientes 15-20: Se refieren al método de preparación de las suspensiones reclamadas en las reivindicaciones 1-13.

D2, enseña métodos de manufactura para obtener las suspensiones en el divulgadas (folio 78 , columna 5 renglones 39-67, columna 6 1-67; folio 79, columna 7 y 8, folio 80 , columna 9 y 10) , en donde se combina: a) **el principio activo** con un primer **agente de suspensión**, b) un **segundo agente de suspensión y un surfactante**; luego además de los ingredientes principales mencionados es también deseable la presencia de ingredientes secundarios entre otros como los **modificadores de pH** (amortiguadores) (folio 79, columna 7, renglones 56-60).

El método de preparación reclamado en la reivindicación 14, no permite evidenciar ningún salto inventivo con respecto a los métodos de fabricación conocidos en el arte previo, como los enseñados en (**D2**).

Por lo tanto las reivindicaciones 14-20, no tienen Nivel inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US2002/0028794	1-20	Nivel Inventivo
D2	US5712310	1-20	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO No.2108	EXAMINADOR TÉCNICO Código No.202078
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