

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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SUPERINDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E.

S.

D.

Re: Expediente No. 00.097.406
Solicitud de Patente en nombre de
JOHNSON & JOHNSON CONSUMER COMPANIES, INC.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad JOHNSON & JOHNSON CONSUMER COMPANIES, INC., solicitante de la patente de la referencia, anexo al presente memorial los siguientes documentos:

Copias certificadas de la solicitudes de Patentes Números 60/172,085 y 09/481,178 presentadas en los Estados Unidos de América los días 23 de diciembre de 1999 y 12 de enero de 2000, respectivamente, con las debidas traducciones de lo pertinente, incluyendo el capítulo reivindicatorio.

A este mismo respecto, debe tenerse en cuenta que en las primeras páginas de las copias en mención la Oficina de Patentes correspondiente certificó la fecha de presentación de esas solicitudes, cumpliéndose de esta forma todos y cada uno de los requisitos establecidos en el inciso segundo del artículo 10 de la Decisión 486 de la Comisión de la Comunidad Andina.

Señor Superintendente,



JIMENA ESCOBAR URIBE

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T.P. 68228

Cód. 5376

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE
LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Febrero 6, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 60/172,085

Fecha de Presentación: Diciembre 23, 1999

**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) P. R. GRANT
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

REIVINDICACIONES

1.- Un método para preparar una película soluble en agua, el método comprende los pasos de (a) preparar una solución que comprende (i) un formador de película seleccionado del grupo que consiste en ácidos poliacrílicos, derivados de celulosa, óxido de polietileno, alcohol polivinílico, y cualquier combinación de los anteriores, (ii) un plastificante soluble en agua que tiene por lo menos un grupo hidroxilo, amido o amino y un punto de ebullición de más de alrededor de 150°C, (iii) un agente farmacéuticamente activo, y (iv) un solvente; (b) secar la solución a una temperatura de alrededor de 50 y aproximadamente 100°C para formar una película; y (c) curar la película a una temperatura de alrededor de 15 a aproximadamente 60°C y a una humedad relativa de por lo menos aproximadamente 30%.

2.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución tiene una viscosidad de alrededor de 15,000 a aproximadamente 30,000 cps a temperatura ambiente antes de secar.

3.- El método de conformidad con la reivindicación 1, caracterizado además porque el formador de película es alcohol polivinílico.

4.- El método de conformidad con la reivindicación 1, caracterizado además porque el formador de película es un alcohol polivinílico parcialmente hidrogenado.

5.- El método de conformidad con la reivindicación 1, caracterizado además porque el plastificante es un compuesto polihidroxi.

6.- El método de conformidad con la reivindicación 5, caracterizado además porque el plastificante se selecciona del grupo que consiste en propilenglicol, polietilenglicol, glicerina, y cualquier combinación de los anteriores.

7.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo se selecciona de agentes antifúngicos de imidazol, agentes antibacterianos, agentes antisépticos, hormonas, agentes antiinflamatorios, anestésicos, espermicidas, y cualquier combinación de los anteriores.

8.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es nonoxinol-9.

9.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es miconazol.

10.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es metronidazol.

11.- El método de conformidad con la reivindicación 1, caracterizado además porque el solvente se selecciona del grupo que consiste en agua, etanol, glicerina, etilenglicol, amidas, aminas y cualquier combinación de los anteriores.

12.- El método de conformidad con la reivindicación 11, caracterizado además porque el solvente es agua.

13.- El método de conformidad con la reivindicación 11, caracterizado además porque el solvente es una mezcla de agua y etanol.

14.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 5 a aproximadamente 40% en peso de formador de película, con base en el 100% en peso total de la solución.

15.- El método de conformidad con la reivindicación 14, caracterizado además porque la solución comprende de alrededor de 15 a aproximadamente 35% en peso de formador de película, con base en el 100% en peso total de la solución.

16.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 0.1 a aproximadamente 10% en peso de plastificante, con base en el 100% en peso total de la solución.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque la solución comprende de alrededor de 0.5 a

aproximadamente 5% en peso de plastificante, con base en el 100% en peso total de la solución.

18.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende una cantidad farmacéuticamente efectiva de agente farmacéuticamente activo.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque la solución comprende de alrededor de 1 a aproximadamente 30% en peso de agente farmacéuticamente activo, con base en el 100% en peso total de la solución.

20.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 20 a aproximadamente 90% en peso de solvente, con base en el 100% en peso total de la solución.

21.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende (a) alrededor de 26.4% en peso de alcohol polivinílico; (b) alrededor de 2.4% en peso de glicerina; (c) alrededor de 11.2% en peso de nonoxinol 9; y (d) alrededor de 60% en peso de agua, con base en el 100% en peso total de la solución.

22.- El método de conformidad con la reivindicación 1, caracterizado además porque la película soluble en agua también comprende (i) una agente tensioactivo, (ii) un conservador, (iii) un incrementador de viscosidad, (iv) un colorante, (v) una fragancia, (vi) un saborizante, (vii) un lubricante, (viii) un llenador, (ix) un aglutinante, (x) un agente humectante, (xi)

un agente de penetración, (xii) un ajustador de pH, (xiii) un desintegrador, (xiv) un excipiente, o (xv) cualquier combinación de los anteriores.

23.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de secado comprende (i) calentar la solución a alrededor de 50 y aproximadamente 70°C; y (ii) calentar la solución a alrededor de 70 y aproximadamente 100°C.

24.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una temperatura de alrededor de 25 a aproximadamente 60°C.

25.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una humedad relativa de por lo menos aproximadamente 50%.

26.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una humedad relativa de alrededor de 60 a aproximadamente 90%.

27.- El método de conformidad con la reivindicación 1, caracterizado además porque la película soluble en agua tiene un espesor de alrededor de 0.03 a aproximadamente 0.50 mm.

28.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso (a) consiste en (i) preparar una solución que comprende (i) un formador de película seleccionado del grupo que consiste en ácidos poliacrílicos, derivados de celulosa, óxido de polietileno, alcohol polivinílico, y cualquier combinación de los anteriores, (ii) un

plastificante soluble en agua que tiene por lo menos un grupo hidroxilo, amido o amino y un punto de ebullición de más de alrededor de 150°C, (iii) un agente farmacéuticamente activo, y (iv) un solvente; y (ii) verter o vaciar la solución en un substrato.

29.- El método de conformidad con la reivindicación 28, caracterizado además porque el substrato es algodón o fibra no tejida.

30.- Una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

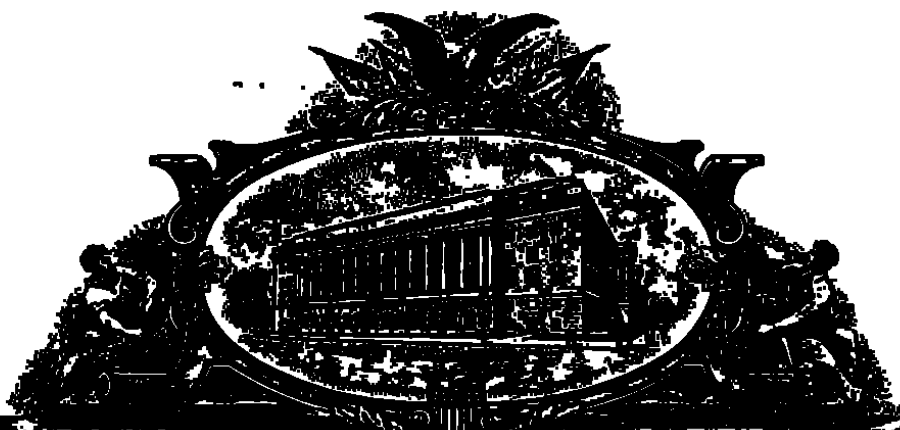
31.- Una forma de dosificación unitaria que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

32.- Un tampón que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

33.- Un aplicador que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

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THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 06, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/172,085

FILING DATE: *December 23, 1999*



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. R. GRANT
Certifying Officer

EXPRESS MAIL CERTIFICATE

Date: 12/23/99 Label No. 595860332

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WITH RESPECT TO THIS APPLICATION TO OUR
DEPOSIT ACCOUNT NO. 04-0100

1-541 U.S. PTO
60/172085
38/31/99

DARBY & DARBY P.C.

808 Third Avenue
New York, New York 10022
212-527-7700

File No: 2092/0G279

Date: December 23, 1999

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Enclosed please find a provisional application for United States patent as identified below:

Inventor/s (ALL inventors, including NAME, plus city and state of RESIDENCE for each):

- | | |
|--|--|
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Title: METHOD OF PREPARING A WATER SOLUBLE FILM

including the items indicated:

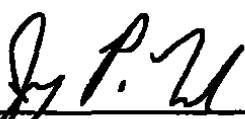
1. Specification and 33 claims: 1 indep.; 32 dep.; multiple dep.

PROVISIONAL PATENT APPLICATION COVER SHEET

2. Check in the amount of \$150.00.

December 23, 1999

Respectfully submitted,



Jay P. Lessler

Reg. No. 41,151

Attorney for Applicant(s)

60172085-122399

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2092/OG279

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METHOD OF PREPARING A WATER SOLUBLE FILM10 **FIELD OF THE INVENTION**

The present invention relates to a method of preparing a water soluble film for use in dosage unit forms, such as tampons and applicators.

BACKGROUND OF THE INVENTION

15 Current vaginal dosage forms, except the sponge and film, are messy to use and readily drip out of the vagina. Furthermore, the sponge requires removal after use and is believed to cause infection. Films often cause irritation due to their rigidity and sharp edges.

U.S. Patent Nos. 5,393,528 and 5,529,782 disclose a device having a dissolvable element for administration of an agent material in an internal body area. The
20 dissolvable element is a film made of polyvinyl alcohol, polyethylene oxide, and/or a complex carbohydrate material.

SUMMARY OF THE INVENTION

The present invention provides a method of preparing a water soluble film.
25 The method comprises the steps of (a) preparing a solution comprising a film former, a water

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soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and a relative humidity of at least about 30%.

The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl

alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. The formulation of the film may be optimized as known in the art to provide controlled release of the pharmaceutically active agent.

This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

Another embodiment of the present invention is a dosage unit form, such as a tampon or applicator, comprising a water soluble film prepared by the aforementioned method.

DETAILED DESCRIPTION OF THE INVENTION

The method of the present invention comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The inventors have discovered that curing the film under the aforementioned conditions produces a significantly more flexible film which drips less when administered into the vagina and other body cavities than the same film prepared without curing. The film is also non-messy, uniform, and homogeneous.

The solution may be prepared by mixing the ingredients, if the pharmaceutically active agent is water soluble.

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Water insoluble pharmaceutically active agents may be dispersed, preferably uniformly, in the solvent by any method known in the art. The other ingredients may be added before or after dispersing the pharmaceutically active agent.

The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. Suitable cellulose derivatives include, but are not limited to, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and any combination of any of the foregoing. The film former is preferably polyvinyl alcohol. More preferably, the film former is a partially hydrogenated polyvinyl alcohol, such as Elvanol™ grade 51-05, 52-22, and 50-42 available from DuPont Co. of Wilmington, DE, and Airvol™ grade 205S and 523S available from Air Products & Chemicals, Inc., of Allentown, PA. The viscosity of the polyvinyl alcohol generally ranges from about 3 to about 1000 cps and preferably ranges from about 3 to about 50 cps. The solution typically comprises from about 5 to about 40% by weight and preferably from about 15 to about 35% by weight of film former, based upon 100% total weight of solution.

The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. Preferably, the boiling point of the plasticizer is greater than about 180° C. Suitable plasticizers include, but are not limited to, polyhydroxy compounds, such as propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing. Other suitable plasticizers include, but are not limited to, fatty acid derivatives having a melting point less than about 45° C, such as hydrogenated vegetable oil available as Wecobee™ from Stepan Company of Northfield, IL, and hydrogenated coco-glycerides available as Witpsol H15™ from Hüls America of Somerset, N.J.; and fatty alcohol derivatives having a hydroxy value of greater than about 30. The solution typically comprises from about 0.1 to about 10% by weight and preferably from about 0.5 to about 5% by weight of water soluble plasticizer, based upon 100% total weight of solution.

The pharmaceutically active agent may be water-insoluble or water soluble. Suitable pharmaceutically active agents include, but are not limited to, imidazole antifungal agents, such as imidazole antifungal agents include, but are not limited to, miconazole,

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econazole, terconazole, ketoconazole, saperconazole, itraconazole, clotrimazole, tioconazole, and butaconazole; antibacterial agents, such as nystatin, neomycin, polymycin, tetracycline, clindamycin, and metronidazole; antiseptic agents, such as oxyquinoline benzoate and aminacrine; hormones, such as estrogens, testolactone, androgens, progestins, megestrol acetate, medroxyprogesterone acetate, esterified estrogens, conjugated estrogens, estradiol, polyestradiol, ethinyl estradiol, estropipate, diethylstilbestrol diphosphate, polyestradiol phosphate, and leuprolide acetate; anti-inflammatory agents, hydrocortisone, triamcinolone, betamethasone, flucinonide, and halcinonide; anesthetics, such as lidocaine and benzocaine; spermicides, such as nonoxynol-9 and octoxynol-9; and any combination of any of the foregoing. A preferred imidazole antifungal agent is miconazole nitrate. A preferred antibacterial agent is metronidazole. A preferred spermicide is nonoxynol-9.

Generally, the amount of pharmaceutically active agent in the solution is an amount effective to accomplish the purpose for which it is being used. The amount of pharmaceutically active agent is typically a pharmaceutically effective amount. However, the amount can be less than a pharmaceutically effective amount when the film is used in a dosage unit form, because the dosage unit form may contain a multiplicity of films or may contain a divided pharmaceutically effective amount. The total effective amount can then be determined in cumulative units containing, in total, a pharmaceutically effective amount of pharmaceutically active agent. The total amount of pharmaceutically active agent may be determined by those skilled in the art. Generally, the solution comprises from about 1 to about 30% by weight and preferably from about 5 to about 20% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

The solvent may be water, ethanol, glycerin, ethylene glycol, amides, amines, or any combination of any of the foregoing. The solvent is preferably water or a mixture of water and ethanol. Preferably, the mixture comprises less than about 30% by weight of ethanol, based upon 100% total weight of mixture. The solution typically comprises from about 20 to about 90% by weight and preferably from about 40 to about 80% by weight of solvent, based upon 100% total weight of solution.

According to a preferred embodiment of the present invention, the solution comprises about 26.4% by weight of polyvinyl alcohol, about 2.4% by weight of glycerin,

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about 11.2% by weight of nonoxynol 9, and about 60% by weight of water, based upon 100% total weight of solution.

The solution may include other adjuvants, such as surfactants, preservatives, viscosity enhancers, colorants, fragrances, flavorants, lubricants, fillers, binders, wetting agents, penetration agents, pH adjusters, disintegrants, excipients, or any combination of any of the foregoing. Suitable surfactants include, but are not limited to, polyethylene glycol ether of cetearyl alcohol, such as cetareth-20; hydrogenated coco-glycerides; and any combination of any of the foregoing.

The solution typically has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying. Generally, the water soluble film prepared by the method of the present invention has a thickness of from about 0.03 to about 0.50 mm. Preferably, the thickness of the film is from about 0.05 to about 0.10 mm.

The drying step is generally performed at a temperature of from about 50 to about 100° C. Preferably, the drying step is performed in two stages. In the first stage, the solution is heated to from about 50 to about 70° C. The solution in the first stage is typically heated for less than about 5 minutes. The solution is then heated to from about 70 to about 100° C during the second stage. The solution in the second stage is typically heated for less than about 25 minutes.

The curing step is preferably performed immediately after the drying step.

Curing is generally performed at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. Preferably, the curing step is performed at a temperature of from about 25 to about 60° C. The curing step is preferably performed at a relative humidity of at least about 50% and more preferably at a relative humidity of from about 60 to about 90%. The solution may be dried and cured with a drying tunnel having multiple zones or chambers, such as a 5, 6, or 7 zone drying tunnel.

A preferred water soluble film prepared by the method of the present invention comprises about 66% by weight of polyvinyl alcohol, about 6% by weight of glycerin, and about 28% by weight of nonoxynol 9, based upon 100% total weight of water soluble film.

The water soluble film may be coated or laminated onto a substrate, such as non-woven fiber or cotton, by pouring or casting the solution onto the substrate and then

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drying and curing the solution as described above. Casting may be performed by any method known in the art, such as with a weigh boat, stainless steel tray, teflon rod, cone shape rod, and reverse roller.

5 The water soluble film alone or coated or laminated on a substrate may be incorporated into a dosage unit form for administration into a body cavity, such as the vagina, rectum, and mouth. The dosage unit form may be a tampon or an applicator. For example, the film coated on a substrate may be utilized as a liner for a tampon. The dosage unit form is preferably flexible. The dosage unit form may be any shape, such as a flat sheet or thimble shape. Preferably, the film is contoured to maximize its contact area with the body cavity for
10 which it is intended to be administered.

According to one embodiment, the outer wrap of the tampon is comprised of non-woven fiber laminated with the water soluble film. According to another embodiment, the water soluble film is positioned between the inside material of a tampon, such as cotton, and an outer wrap, such as a non-woven fiber material.

15 A dosage unit form of the present invention containing an antifungal agent, such as miconazole, may be administered to treat yeast infections. It is possible to treat a yeast infection in 3 days, instead of the common 5 day period, with a dosage unit form of the present invention, since a film prepared by the present method has very little drip and may have controlled release of the antifungal agent.

20 The film may be formulated to be puncture resistant and tear resistant. Also, the film may be formulated to achieve desired release rates of the pharmaceutically active agent as known in the art.

25 The following examples are intended to describe the present invention without limitation.

Examples 1-32

Water soluble films having the formulations of Table 1 were prepared as follows. Water was heated to 50-80° C. The film former, i.e., polyvinyl alcohol, is added to
30 the water with constant mixing. The active ingredient, i.e., nonoxynol-9, was added to the

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solution with constant mixing. The solution was mixed, deaerated, and cooled to room temperature. The solution was coated onto a substrate in the casting device indicated in Table 1 below. The substrate for Examples 1-8 was polypropylene. The substrate for Examples 9-18 and 32 was stainless steel. The substrate for Examples 19-25 was polyester. The substrate for Examples 26-28 was teflon. The substrate for Example 29 was a polyester liner. The substrate for Example 30 was aclar with foil liner. The substrate for Example 31 was a polyethylene and paper liner.

The solution was dried in a multi-zone drying tunnel to form a film. In Examples 1-28 and 31, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Examples 29 and 30, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. In Example 32, the solution was first dried at a temperature of about 60-80° C for less than about 5 minutes and then dried at a temperature of about 70-90° C for less than about 25 minutes.

After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. For examples 29 and 32, the film was cured with moisture at a relative humidity of about 60-90% and at a temperature of about 40-60° C.

The thickness of the film was measured. The results are shown in Table 1 below.

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Table 1

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
1	Weigh Boat	33.33	33.33	-	-	33.33% PG	0.3
2	Weigh Boat	33.33	33.33	-	-	33.33% PEG 300	0.3
3	Weigh Boat	33.33	50.00	-	-	16.67% PEG 300	0.45
4	Weigh Boat	33.33	58.33	-	-	8.33% Glycerin	0.3
5	Weigh Boat	33.33	41.67	-	-	25.00% Glycerin	0.1
6	Weigh Boat	33.33	50.00	-	-	16.67% Glycerin	0.1
7	Weigh Boat	33.33	50.00	-	-	16.67% PG	0.2
8	Weigh Boat	33.33	41.67	-	-	25.00% PG	0.1
9	Stainless Steel Tray	33.00	58.67	-	-	8.33% Glycerin	0.07
10	Stainless Steel Tray	33.33	63.33	-	-	3.33% Glycerin	0.05

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
11	Stainless Steel Tray	33.33	58.33	-	-	8.33% PEG 300	-
12	Stainless Steel Tray	33.33	58.67	-	-	8.33% PG	0.06
13	Stainless Steel Tray	27.78	69.44	-	-	2.78% Glycerin	-
14	Stainless Steel Tray	33.33	-	-	58.33	8.33% Glycerin	0.06
15	Stainless Steel Tray	32.79	-	-	49.18	18.03% Glycerin	0.07
16	Stainless Steel Tray	33.33	-	-	41.67	25.00% Glycerin	-
17	Stainless Steel Tray	33.33	-	-	63.33	3.33% Glycerin	0.07

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
18	Stainless Steel Tray	28.33	-	-	68.00	3.67% Glycerin	-
19	Resource I'	33.33	-	58.33	-	8.33% Glycerin	-
20	Resource I'	33.11	-	62.913	-	3.97% Glycerin	-
21	Resource I'	33.33	-	49.50	-	17.16% Glycerin	-
5 22	Resource I'	33.33	-	-	63.35	3.33% Glycerin	-
23	Resource I'	33.33	50.00	-	-	16.33% PEG 300	-
24	Resource I'	33.33	58.33	-	-	8.33% PEG 300	-
25	Resource I'	33.33	63.33	-	-	3.33% PEG 300	-
26	Teflon Rod, Thimble	33.33	-	-	63.35	3.33% Glycerin	-
10 27	Cone Shape Rod, Thimble	31.58	-	-	60.00	3.16% Glycerin & 5.26% H-15	-

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Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
28	Cone Shape Rod, Thimble	30.51	-	-	57.97	3.05% Glycerin & 8.47% H-15	-
29	Reverse Roller, Scale-up Run, with Polyester Liner	33.33	-	-	63.33	3.33% Glycerin	-
30	Reverse Roller, Scale-up Run, with Aclar and Foil Liner	33.33	-	-	63.36	3.30% Glycerin	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
31	Knife Over Roller, Scale-up Run, with Polyethylene and Paper Liner	28.00	-	-	67.00	5.00% Glycerin	-
32	Extrusion, Scale-up Run, with Stainless Steel Surface Carrier	28.00	-	-	67.00	5.00% Glycerin	-

* - Resource I is a casting device for solutions available from Byk-Gardner Instruments of Silver Spring, MD.

- 5 The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

PG is propylene glycol.

PEG 300 is polyethylene glycol having an average of 300 ethylene oxide repeating units.

H-15 is Witpsol H-15, which is hydrogenated coco-glycerides and is available from Hüls America of Somerset, NJ.

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The release rate of nonoxynol-9 from the films prepared and VCF[®] available from Apothecus Pharmaceutical Corp. of Oyster Bay, NY, in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method (United States Pharmacopeia Method Section <711>). The results are shown in Table 2 below. The time to plateau is the time after which there is no significant increase in the release rate.

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Table 2

Formulation	Time to Plateau (minutes)	Release Rate (% by weight per minute)
VCF ¹	15-20	5.45
Example 6	50-60	2.59
Example 7	50-60	3.76
Example 9	40-50	2.33
Example 10	40-50	2.97
Example 12	40-50	3.15
Example 14	10-15	6.08
Example 15	10-15	6.66
Example 17	10-15	6.01
Example 19	15-20	5.82
Example 20	30-40	4.33
Example 21	30-40	3.93
Example 22	10-15	6.10
Example 23	40-50	2.34
Example 24	30-40	2.72
Example 25	30-40	2.76
Example 26	10-15	7.23
Example 27	5-10	8.47
Example 28	5-10	8.89
Example 29	<15	>6.0
Example 30	<15	>6.0
Example 31	<15	>6.0
Example 32	<15	>16

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Examples 33-42

Water soluble films having the formulations of Table 3 were prepared as described in Examples 1-32. In Examples 33-41, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Example 42, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature.

The substrate for Examples 33-35 was polyester. The substrate for Examples 36-41 was polyester and non-woven fiber. The substrate for Example 42 was a fiber and polyester liner.

The release rate of nonoxynol-9 from the films prepared in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method for Examples 33-35 and by the following modified USP method for Examples 36-38, 40, and 41. A dialysis membrane with known molecular weight cut-off and diameter was used instead of a mesh basket for holding the test samples. The membrane limited the amount of dissolution medium which contacted the release layer or composition. This modified dissolution procedure was designed to mimic a vaginal environment where only limited amounts of a medium are typically in contact with the composition. Each release layer and composition was tested in an aqueous medium and in a buffered aqueous medium, which were maintained at a pH of about 4.

The results are shown in Table 3 below.

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Table 3

Example	Casting Device	Polyvinyl alcohol (<30 cps) (% by weight)	Plasticizer (% by weight)	Miconazole Nitrate (% by weight)	Release Rate
33	Resource I	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.3%/min
34	Resource I	40.0	19.9% Glycerin	40.1	4.7%/min
35	Resource I	38.0	19.0% Glycerin & 4.8% EB2	38.2	4.7%/min
36	Resource I & Fiber	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.50%/hr
37	Resource I & Fiber	34.7	17.3% Glycerin & 13.2% EB2	34.8	3.13%/hr
38	Resource I & Fiber	38.0	19.0% Glycerin & 5.0% EB2	38.0	3.33%/hr
39	Resource I & Fiber	39.6	20.6% Glycerin	39.8	-
40	Resource I, Fiber, & OB Tampon	34.7	17.3% Glycerin & 13.2% EB2	34.8	0.81%/hr
41	Resource I, Fiber, & OB Tampon	38.0	19.0% Glycerin & 5.0% EB2	38.0	1.07%/hr
42	Reverse Roller, Scale-up Run, Fiber & Polyester Liner	38.1	19.1% Glycerin & 4.7% EB2	38.1	-

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EB2 is Eumulgin B2, which is cetcareth-20 and is available from Henkel Corp. of Hoboken, NJ.

The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

Examples 43-46

Water soluble films having the formulations of Table 4 were prepared as described in Examples 1-32. In Examples 43-46, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. The substrate for Example 43-46 was polyester.

The time for the dissolution rate to plateau was determined as discussed above.

The results are shown in Table 4 below.

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Table 4

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro- nidazole (% by weight)	Dissolution (Time to Plateau) (min)
43	Resource I	67.2% PVA 52-22	21.7% PEG 400	11.1	20-30
44	Resource I	58.22% PVA 52-22	18.9% PG & 15.7% EB2	7.2	20-30
45	Resource I	34.9% PVA 52-22 and 11.7% PVA 71-30	20.9% PG & 17.5% EB2	15.0	10-15
46	Resource I	46.6% HPMC E50LV	20.9% PG & 17.5% EB2	15.0	5-10

PG is propylene glycol

PEG is polyethylene glycol.

EB2 is Emulgin B2, which is cetareth-20 and is available from Henkel Corp. of Hoboken, NJ.

PVA is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

HPMC is hydroxypropyl methylcellulose.

Example 47

A water soluble film having the formulation of Table 5 was prepared as follows. Glycerin and nonoxynol-9 were added into cold water and mixed until uniform. The solution was heated to about 60-80° C and the film former, i.e., polyvinyl alcohol, was added under constant mixing. The solution was mixed, deaerated, and cooled to about room

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temperature. The solution was coated onto a stainless steel surface with a web thickness of 0.01 to 0.03 cm. The solution was dried in a multi-zone drying tunnel at a temperature of about 60-90° C for less than about 30 minutes to form a film. The film was then cured with moisture at a relative humidity of about 65-90% and at a temperature of about 40-60° C.

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Table 5

Ingredient	% by weight
Polyvinyl Alcohol (5 cps)	66.0
Glycerin	6.0
Nonoxynol-9	28.0

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All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

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What is claimed is:

1. A method of preparing a water soluble film, the method comprising the steps of

(a) preparing a solution comprising

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent;

(b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and

(c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%.

2. The method of claim 1, wherein the solution has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying.

3. The method of claim 1, wherein the film former is polyvinyl alcohol.

4. The method of claim 1, wherein the film former is a partially hydrogenated polyvinyl alcohol.

5. The method of claim 1, wherein the plasticizer is a polyhydroxy compound.

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6. The method of claim 5, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing.

7. The method of claim 1, wherein the pharmaceutically active agent is selected from imidazole antifungal agents, antibacterial agents, antiseptic agents, hormones, anti-inflammatory agents, anesthetics, spermicides, and any combination of any of the foregoing.

8. The method of claim 1, wherein the pharmaceutically active agent is nonoxynol-9.

9. The method of claim 1, wherein the pharmaceutically active agent is miconazole.

10. The method of claim 1, wherein the pharmaceutically active agent is metronidazole.

11. The method of claim 1, wherein the solvent is selected from the group consisting of water, ethanol, glycerin, ethylene glycol, amides, amines, and any combination of any of the foregoing.

12. The method of claim 11, wherein the solvent is water.

13. The method of claim 11, wherein the solvent is a mixture of water and ethanol.

14. The method of claim 1, wherein the solution comprises from about 5 to about 40% by weight of film former, based upon 100% total weight of solution.

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15. The method of claim 14, wherein the solution comprises from about 15 to about 35% by weight of film former, based upon 100% total weight of solution.

16. The method of claim 1, wherein the solution comprises from about 0.1 to about 10% by weight of plasticizer, based upon 100% total weight of solution.

17. The method of claim 16, wherein the solution comprises from about 0.5 to about 5% by weight of plasticizer, based upon 100% total weight of solution.

18. The method of claim 1, wherein the solution comprises a pharmaceutically effective amount of pharmaceutically active agent.

19. The method of claim 18, wherein the solution comprises from about 1 to about 30% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

20. The method of claim 1, wherein the solution comprises from about 20 to about 90% by weight of solvent, based upon 100% total weight of solution.

21. The method of claim 1, wherein the solution comprises
(a) about 26.4% by weight of polyvinyl alcohol;
(b) about 2.4% by weight of glycerin;
(c) about 11.2% by weight of nonoxynol 9; and
(d) about 60% by weight of water,
based upon 100% total weight of solution.

22. The method of claim 1, wherein the water soluble film further comprises

(i) a surfactant,
(ii) a preservative,

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- (iii) a viscosity enhancer,
- (iv) a colorant,
- (v) a fragrance,
- (vi) a flavorant,
- (vii) a lubricant,
- (viii) a filler,
- (ix) a binder,
- (x) a wetting agent,
- (xi) a penetration agent,
- (xii) a pH adjuster,
- (xiii) a disintegrant,
- (xiv) an excipient, or
- (xv) any combination of any of the foregoing.

23. The method of claim 1, wherein the drying step comprises

- (i) heating the solution to from about 50 to about 70° C; and
- (ii) heating the solution to from about 70 to about 100° C.

24. The method of claim 1, wherein the curing step is performed at a temperature of from about 25 to about 60° C.

25. The method of claim 1, wherein the curing step is performed at a relative humidity of at least about 50%.

26. The method of claim 1, wherein the curing step is performed at a relative humidity of from about 60 to about 90%.

27. The method of claim 1, wherein the water soluble film has a thickness of from about 0.03 to about 0.50 mm.

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28. The method of claim 1, wherein step (a) comprises

(i) preparing a solution comprising

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent; and

(ii) pouring or casting the solution on a substrate.

29. The method of claim 28, wherein the substrate is cotton or non-woven fiber.

30. A water soluble film prepared by the method of claim 1.

31. A dosage unit form having a water soluble film prepared by the method of claim 1.

32. A tampon having a water soluble film prepared by the method of claim 1.

33. An applicator having a water soluble film prepared by the method of claim 1.

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ABSTRACT

The present invention provides a method of preparing a water soluble film.

5 The method comprises (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivatives, polyethylene oxide, polyvinyl
10 alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

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Enero 11, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 09/481,178

Fecha de Presentación: Enero 12, 2000

**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) P.R. GRANT
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un método para preparar una película soluble en agua, el método comprende los pasos de (a) preparar una solución que comprende (i) un formador de película seleccionado del grupo que consiste en ácidos poliacrílicos, derivados de celulosa, óxido de polietileno, alcohol polivinílico, y cualquier combinación de los anteriores, (ii) un plastificante soluble en agua que tiene por lo menos un grupo hidroxilo, amido o amino y un punto de ebullición de más de alrededor de 150°C, (iii) un agente farmacéuticamente activo, y (iv) un solvente; (b) secar la solución a una temperatura de alrededor de 50 y aproximadamente 100°C para formar una película; y (c) curar la película a una temperatura de alrededor de 15 a aproximadamente 60°C y a una humedad relativa de por lo menos aproximadamente 30%.

2.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución tiene una viscosidad de alrededor de 15,000 a aproximadamente 30,000 cps a temperatura ambiente antes de secar.

3.- El método de conformidad con la reivindicación 1, caracterizado además porque el formador de película es alcohol polivinílico.

4.- El método de conformidad con la reivindicación 1, caracterizado además porque el formador de película es un alcohol polivinílico parcialmente hidrogenado.

5.- El método de conformidad con la reivindicación 1, caracterizado además porque el plastificante es un compuesto polihidroxi.

6.- El método de conformidad con la reivindicación 5, caracterizado además porque el plastificante se selecciona del grupo que consiste en propilenglicol, polietilenglicol, glicerina, y cualquier combinación de los anteriores.

7.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo se selecciona de agentes antifúngicos de imidazol, agentes antibacterianos, agentes antisépticos, hormonas, agentes antiinflamatorios, anestésicos, espermicidas, y cualquier combinación de los anteriores.

8.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es nonoxinol-9.

9.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es miconazol.

10.- El método de conformidad con la reivindicación 1, caracterizado además porque el agente farmacéuticamente activo es metronidazol.

11.- El método de conformidad con la reivindicación 1, caracterizado además porque el solvente se selecciona del grupo que consiste en agua, etanol, glicerina, etilenglicol, amidas, aminas y cualquier combinación de los anteriores.

12.- El método de conformidad con la reivindicación 11, caracterizado además porque el solvente es agua.

13.- El método de conformidad con la reivindicación 11, caracterizado además porque el solvente es una mezcla de agua y etanol.

14.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 5 a aproximadamente 40% en peso de formador de película, con base en el 100% en peso total de la solución.

15.- El método de conformidad con la reivindicación 14, caracterizado además porque la solución comprende de alrededor de 15 a aproximadamente 35% en peso de formador de película, con base en el 100% en peso total de la solución.

16.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 0.1 a aproximadamente 10% en peso de plastificante, con base en el 100% en peso total de la solución.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque la solución comprende de alrededor de 0.5 a

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aproximadamente 5% en peso de plastificante, con base en el 100% en peso total de la solución.

18.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende una cantidad farmacéuticamente efectiva de agente farmacéuticamente activo.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque la solución comprende de alrededor de 1 a aproximadamente 30% en peso de agente farmacéuticamente activo, con base en el 100% en peso total de la solución.

20.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende de alrededor de 20 a aproximadamente 90% en peso de solvente, con base en el 100% en peso total de la solución.

21.- El método de conformidad con la reivindicación 1, caracterizado además porque la solución comprende (a) alrededor de 26.4% en peso de alcohol polivinílico; (b) alrededor de 2.4% en peso de glicerina; (c) alrededor de 11.2% en peso de nonoxinol 9; y (d) alrededor de 60% en peso de agua, con base en el 100% en peso total de la solución.

22.- El método de conformidad con la reivindicación 1, caracterizado además porque la película soluble en agua también comprende (i) una agente tensioactivo, (ii) un conservador, (iii) un incrementador de viscosidad, (iv) un colorante, (v) una fragancia, (vi) un saborizante, (vii) un lubricante, (viii) un llenador, (ix) un aglutinante, (x) un agente humectante, (xi)

un agente de penetración, (xii) un ajustador de pH, (xiii) un desintegrador, (xiv) un excipiente, o (xv) cualquier combinación de los anteriores.

23.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de secado comprende (i) calentar la solución a alrededor de 50 y aproximadamente 70°C; y (ii) calentar la solución a alrededor de 70 y aproximadamente 100°C.

24.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una temperatura de alrededor de 25 a aproximadamente 60°C.

25.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una humedad relativa de por lo menos aproximadamente 50%.

26.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso de curación se lleva a cabo a una humedad relativa de alrededor de 60 a aproximadamente 90%.

27.- El método de conformidad con la reivindicación 1, caracterizado además porque la película soluble en agua tiene un espesor de alrededor de 0.03 a aproximadamente 0.50 mm.

28.- El método de conformidad con la reivindicación 1, caracterizado además porque el paso (a) consiste en (i) preparar una solución que comprende (i) un formador de película seleccionado del grupo que consiste en ácidos poliacrílicos, derivados de celulosa, óxido de polietileno, alcohol polivinílico, y cualquier combinación de los anteriores, (ii) un

plastificante soluble en agua que tiene por lo menos un grupo hidroxilo, amido o amino y un punto de ebullición de más de alrededor de 150°C, (iii) un agente farmacéuticamente activo, y (iv) un solvente; y (ii) verter o vaciar la solución en un sustrato.

29.- El método de conformidad con la reivindicación 28, caracterizado además porque el sustrato es algodón o fibra no tejida.

30.- Una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

31.- Una forma de dosificación unitaria que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

32.- Un tampón que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

33.- Un aplicador que tiene una película soluble en agua preparada mediante el método de conformidad con la reivindicación 1.

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January 11, 2001

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APPLICATION NUMBER: 09/481,178

FILING DATE: January 12, 2000



**By Authority of the
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A handwritten signature in cursive script, appearing to read "P. R. Grant", is written over the printed name.

**P. R. GRANT
Certifying Officer**

1-13-00

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File No: 2092/1G279-US1

Date: January 12, 2000

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Enclosed please find an application for United States patent as identified below:

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Title: METHOD OF PREPARING A WATER SOLUBLE FILM

including the items indicated:

1. Specification and 33 claims: 1 indep.; 32 dep.; multiple dep.; and

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2. Unsigned Declaration and Power of Attorney.

January 12, 2000

Respectfully submitted,



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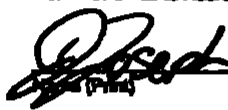
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5 **METHOD OF PREPARING A WATER SOLUBLE FILM**

This application claims priority from U.S. Serial No. 60/172,085, filed December 23, 1999, which is incorporated herein by reference.

10 **FIELD OF THE INVENTION**

The present invention relates to a method of preparing a water soluble film for use in dosage unit forms, such as tampons and applicators.

BACKGROUND OF THE INVENTION

15 Current vaginal dosage forms, except the sponge and film, are messy to use and readily drip out of the vagina. Furthermore, the sponge requires removal after use and is believed to cause infection. Films often cause irritation due to their rigidity and sharp edges.

U.S. Patent Nos. 5,393,528 and 5,529,782 disclose a device having a dissolvable element for administration of an agent material in an internal body area. The
20 dissolvable element is a film made of polyvinyl alcohol, polyethylene oxide, and/or a complex carbohydrate material.

SUMMARY OF THE INVENTION

The present invention provides a method of preparing a water soluble film.
25 The method comprises the steps of (a) preparing a solution comprising a film former, a water

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soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and a relative humidity of at least about 30%.

The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. The formulation of the film may be optimized as known in the art to provide controlled release of the pharmaceutically active agent.

This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

Another embodiment of the present invention is a dosage unit form, such as a tampon or applicator, comprising a water soluble film prepared by the aforementioned method.

DETAILED DESCRIPTION OF THE INVENTION

The method of the present invention comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The inventors have discovered that curing the film under the aforementioned conditions produces a significantly more flexible film which drips less when administered into the vagina and other body cavities than the same film prepared without curing. The film is also non-messy, uniform, and homogeneous.

The solution may be prepared by mixing the ingredients, if the pharmaceutically active agent is water soluble.

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Water insoluble pharmaceutically active agents may be dispersed, preferably uniformly, in the solvent by any method known in the art. The other ingredients may be added before or after dispersing the pharmaceutically active agent.

The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. Suitable cellulose derivatives include, but are not limited to, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and any combination of any of the foregoing. The film former is preferably polyvinyl alcohol. More preferably, the film former is a partially hydrogenated polyvinyl alcohol, such as Elvanol™ grade 51-05, 52-22, and 50-42 available from DuPont Co. of Wilmington, DE, and Airvol™ grade 205S and 523S available from Air Products & Chemicals, Inc., of Allentown, PA. The viscosity of the polyvinyl alcohol generally ranges from about 3 to about 1000 cps and preferably ranges from about 3 to about 50 cps. The solution typically comprises from about 5 to about 40% by weight and preferably from about 15 to about 35% by weight of film former, based upon 100% total weight of solution.

The water soluble plasticizer contains at least one of a hydroxyl, amide, or amino group and has a boiling point greater than about 150° C. Preferably, the boiling point of the plasticizer is greater than about 180° C. Suitable plasticizers include, but are not limited to, polyhydroxy compounds, such as propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing. Other suitable plasticizers include, but are not limited to, fatty acid derivatives having a melting point less than about 45° C, such as hydrogenated vegetable oil available as Wecobee™ from Stepan Company of Northfield, IL, and hydrogenated coco-glycerides available as Witpsol H15™ from Huls America of Somerset, N.J.; and fatty alcohol derivatives having a hydroxy value of greater than about 30. The solution typically comprises from about 0.1 to about 10% by weight and preferably from about 0.5 to about 5% by weight of water soluble plasticizer, based upon 100% total weight of solution.

The pharmaceutically active agent may be water-insoluble or water soluble. Suitable pharmaceutically active agents include, but are not limited to, imidazole antifungal agents, such as imidazole antifungal agents include, but are not limited to, miconazole,

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econazole, terconazole, ketoconazole, saperconazole, itraconazole, clotrimazole, tioconazole, and butaconazole; antibacterial agents, such as nystatin, neomycin, polymycin, tetracycline, clindamycin, and metronidazole; antiseptic agents, such as oxyquinoline benzoate and aminacrine; hormones, such as estrogens, testolactone, androgens, progestins, megestrol acetate, medroxyprogesterone acetate, esterified estrogens, conjugated estrogens, estradiol, 5 polyestradiol, ethinyl estradiol, estropipate, diethylstilbestrol diphosphate, polyestradiol phosphate, and leuprolide acetate; anti-inflammatory agents, hydrocortisone, triamcinolone, betamethasone, flucinonide, and halcinonide; anesthetics, such as lidocaine and benzocaine; spermicides, such as nonoxynol-9 and octoxynol-9; and any combination of any of the 10 foregoing. A preferred imidazole antifungal agent is miconazole nitrate. A preferred antibacterial agent is metronidazole. A preferred spermicide is nonoxynol-9.

Generally, the amount of pharmaceutically active agent in the solution is an amount effective to accomplish the purpose for which it is being used. The amount of pharmaceutically active agent is typically a pharmaceutically effective amount. However, the 15 amount can be less than a pharmaceutically effective amount when the film is used in a dosage unit form, because the dosage unit form may contain a multiplicity of films or may contain a divided pharmaceutically effective amount. The total effective amount can then be determined in cumulative units containing, in total, a pharmaceutically effective amount of pharmaceutically active agent. The total amount of pharmaceutically active agent may be 20 determined by those skilled in the art. Generally, the solution comprises from about 1 to about 30% by weight and preferably from about 5 to about 20% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

The solvent may be water, ethanol, glycerin, ethylene glycol, amides, amines, or any combination of any of the foregoing. The solvent is preferably water or a mixture of 25 water and ethanol. Preferably, the mixture comprises less than about 30% by weight of ethanol, based upon 100% total weight of mixture. The solution typically comprises from about 20 to about 90% by weight and preferably from about 40 to about 80% by weight of solvent, based upon 100% total weight of solution.

According to a preferred embodiment of the present invention, the solution 30 comprises about 26.4% by weight of polyvinyl alcohol, about 2.4% by weight of glycerin,

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about 11.2% by weight of nonoxynol 9, and about 60% by weight of water, based upon 100% total weight of solution.

The solution may include other adjuvants, such as surfactants, preservatives, viscosity enhancers, colorants, fragrances, flavorants, lubricants, fillers, binders, wetting agents, penetration agents, pH adjusters, disintegrants, excipients, or any combination of any of the foregoing. Suitable surfactants include, but are not limited to, polyethylene glycol ether of cetearyl alcohol, such as cetareth-20; hydrogenated coco-glycerides; and any combination of any of the foregoing.

The solution typically has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying. Generally, the water soluble film prepared by the method of the present invention has a thickness of from about 0.03 to about 0.50 mm. Preferably, the thickness of the film is from about 0.05 to about 0.10 mm.

The drying step is generally performed at a temperature of from about 50 to about 100° C. Preferably, the drying step is performed in two stages. In the first stage, the solution is heated to from about 50 to about 70° C. The solution in the first stage is typically heated for less than about 5 minutes. The solution is then heated to from about 70 to about 100° C during the second stage. The solution in the second stage is typically heated for less than about 25 minutes.

The curing step is preferably performed immediately after the drying step. Curing is generally performed at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. Preferably, the curing step is performed at a temperature of from about 25 to about 60° C. The curing step is preferably performed at a relative humidity of at least about 50% and more preferably at a relative humidity of from about 60 to about 90%. The solution may be dried and cured with a drying tunnel having multiple zones or chambers, such as a 5, 6, or 7 zone drying tunnel.

A preferred water soluble film prepared by the method of the present invention comprises about 66% by weight of polyvinyl alcohol, about 6% by weight of glycerin, and about 28% by weight of nonoxynol 9, based upon 100% total weight of water soluble film.

The water soluble film may be coated or laminated onto a substrate, such as non-woven fiber or cotton, by pouring or casting the solution onto the substrate and then

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drying and curing the solution as described above. Casting may be performed by any method known in the art, such as with a weigh boat, stainless steel tray, teflon rod, cone shape rod, and reverse roller.

The water soluble film alone or coated or laminated on a substrate may be incorporated into a dosage unit form for administration into a body cavity, such as the vagina, rectum, and mouth. The dosage unit form may be a tampon or an applicator. For example, the film coated on a substrate may be utilized as a liner for a tampon. The dosage unit form is preferably flexible. The dosage unit form may be any shape, such as a flat sheet or thimble shape. Preferably, the film is contoured to maximize its contact area with the body cavity for which it is intended to be administered.

According to one embodiment, the outer wrap of the tampon is comprised of non-woven fiber laminated with the water soluble film. According to another embodiment, the water soluble film is positioned between the inside material of a tampon, such as cotton, and an outer wrap, such as a non-woven fiber material.

A dosage unit form of the present invention containing an antifungal agent, such as miconazole, may be administered to treat yeast infections. It is possible to treat a yeast infection in 3 days, instead of the common 5 day period, with a dosage unit form of the present invention, since a film prepared by the present method has very little drip and may have controlled release of the antifungal agent.

The film may be formulated to be puncture resistant and tear resistant. Also, the film may be formulated to achieve desired release rates of the pharmaceutically active agent as known in the art.

The following examples are intended to describe the present invention without limitation.

Examples 1-32

Water soluble films having the formulations of Table 1 were prepared as follows. Water was heated to 50-80° C. The film former, *i.e.*, polyvinyl alcohol, is added to the water with constant mixing. The active ingredient, *i.e.*, nonoxynol-9, was added to the

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solution with constant mixing. The solution was mixed, deaerated, and cooled to room temperature. The solution was coated onto a substrate in the casting device indicated in Table 1 below. The substrate for Examples 1-8 was polypropylene. The substrate for Examples 9-18 and 32 was stainless steel. The substrate for Examples 19-25 was polyester. The substrate for Examples 26-28 was teflon. The substrate for Example 29 was a polyester liner. The substrate for Example 30 was aclar with foil liner. The substrate for Example 31 was a polyethylene and paper liner.

The solution was dried in a multi-zone drying tunnel to form a film. In Examples 1-28 and 31, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Examples 29 and 30, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. In Example 32, the solution was first dried at a temperature of about 60-80° C for less than about 5 minutes and then dried at a temperature of about 70-90° C for less than about 25 minutes.

After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. For examples 29 and 32, the film was cured with moisture at a relative humidity of about 60-90% and at a temperature of about 40-60° C.

The thickness of the film was measured. The results are shown in Table 1 below.

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Table 1

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
1	Weigh Boat	33.33	33.33	-	-	33.33% PG	0.3
2	Weigh Boat	33.33	33.33	-	-	33.33% PEG 300	0.3
5 3	Weigh Boat	33.33	50.00	-	-	16.67% PEG 300	0.45
4	Weigh Boat	33.33	58.33	-	-	8.33% Glycerin	0.3
5	Weigh Boat	33.33	41.67	-	-	25.00% Glycerin	0.1
6	Weigh Boat	33.33	50.00	-	-	16.67% Glycerin	0.1
7	Weigh Boat	33.33	50.00	-	-	16.67% PG	0.2
10 8	Weigh Boat	33.33	41.67	-	-	25.00% PG	0.1
9	Stainless Steel Tray	33.00	58.67	-	-	8.33% Glycerin	0.07
10	Stainless Steel Tray	33.33	63.33	-	-	3.33% Glycerin	0.05

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
11	Stainless Steel Tray	33.33	58.33	-	-	8.33% PBG 300	-
12	Stainless Steel Tray	33.33	58.67	-	-	8.33% PG	0.06
13	Stainless Steel Tray	27.78	69.44	-	-	2.78% Glycerin	-
14	Stainless Steel Tray	33.33	-	-	58.33	8.33% Glycerin	0.06
15	Stainless Steel Tray	32.79	-	-	49.18	18.03% Glycerin	0.07
16	Stainless Steel Tray	33.33	-	-	41.67	25.00% Glycerin	-
17	Stainless Steel Tray	33.33	-	-	63.33	3.33% Glycerin	0.07

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Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
18	Stainless Steel Tray	28.33	-	-	68.00	3.67% Glycerin	-
19	Resource I'	33.33	-	58.33	-	8.33% Glycerin	-
20	Resource I'	33.11	-	62.913	-	3.97% Glycerin	-
21	Resource I'	33.33	-	49.50	-	17.16% Glycerin	-
22	Resource I'	33.33	-	-	63.35	3.33% Glycerin	-
23	Resource I'	33.33	50.00	-	-	16.33% PEG 300	-
24	Resource I'	33.33	58.33	-	-	8.33% PEG 300	-
25	Resource I'	33.33	63.33	-	-	3.33% PEG 300	-
26	Teflon Rod, Thimble	33.33	-	-	63.35	3.33% Glycerin	-
27	Cone Shape Rod, Thimble	31.58	-	-	60.00	3.16% Glycerin & 5.26% H-15	-

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Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
28	Cone Shape Rod, Thimble	30.51	-	-	57.97	3.05% Glycerin & 8.47% H-15	-
29	Reverse Roller, Scale-up Run, with Polyester Liner	33.33	-	-	63.33	3.33% Glycerin	-
30	Reverse Roller, Scale-up Run, with Aclar and Foil Liner	33.33	-	-	63.36	3.30% Glycerin	-

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Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<50 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
31	Knife Over Roller, Scale-up Run, with Polyethylene and Paper Liner	28.00	-	-	67.00	5.00% Glycerin	-
32	Extrusion, Scale-up Run, with Stainless Steel Surface Carrier	28.00	-	-	67.00	5.00% Glycerin	-

* - Resource I is a casting device for solutions available from Byk-Gardner Instruments of Silver Spring, MD.

- 5 The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

PG is propylene glycol.

PBG 300 is polyethylene glycol having an average of 300 ethylene oxide repeating units.

H-15 is Witexol H-15, which is hydrogenated coco-glycerides and is available from Huls America of Somerset, NJ.

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The release rate of nonoxynol-9 from the films prepared and VCF[®] available from Apothecus Pharmaceutical Corp. of Oyster Bay, NY, in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method (United States Pharmacopeia Method Section <711>). The results are shown in Table 2 below. The time to plateau is the time after which there is no significant increase in the release rate.

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Table 2

	Formulation	Time to Plateau (minutes)	Release Rate (% by weight per minute)
	VCF [®] 1	15-20	5.45
	Example 6	50-60	2.59
5	Example 7	50-60	3.76
	Example 9	40-50	2.33
	Example 10	40-50	2.97
	Example 12	40-50	3.15
	Example 14	10-15	6.08
10	Example 15	10-15	6.66
	Example 17	10-15	6.01
	Example 19	15-20	5.82
	Example 20	30-40	4.33
	Example 21	30-40	3.93
15	Example 22	10-15	6.10
	Example 23	40-50	2.34
	Example 24	30-40	2.72
	Example 25	30-40	2.76
	Example 26	10-15	7.23
20	Example 27	5-10	8.47
	Example 28	5-10	8.89
	Example 29	<15	>6.0
	Example 30	<15	>6.0
	Example 31	<15	>6.0
25	Example 32	<15	>16

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Examples 33-42

Water soluble films having the formulations of Table 3 were prepared as described in Examples 1-32. In Examples 33-41, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Example 42, the solution was first dried at
5 a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature.

The substrate for Examples 33-35 was polyester. The substrate for Examples 36-41 was polyester and non-woven fiber. The substrate for Example 42 was a fiber and
10 polyester liner.

The release rate of miconazole nitrate from the films prepared in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method for Examples 33-35 and by the following modified USP method for Examples 36-38, 40, and 41. A dialysis membrane with known molecular weight cut-off and diameter was used instead of a mesh
15 basket for holding the test samples. The membrane limited the amount of dissolution medium which contacted the release layer or composition. This modified dissolution procedure was designed to mimic a vaginal environment where only limited amounts of a medium are typically in contact with the composition. Each release layer and composition was tested in an aqueous medium and in a buffered aqueous medium, which were maintained at a pH of
20 about 4.

The results are shown in Table 3 below.

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Table 3

Example	Casting Device	Polyvinyl alcohol (<30 cps) (% by weight)	Plasticizer (% by weight)	Miconazole Nitrate (% by weight)	Release Rate
33	Resource I	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.3%/min
34	Resource I	40.0	19.9% Glycerin	40.1	4.7%/min
35	Resource I	38.0	19.0% Glycerin & 4.8% EB2	38.2	4.7%/min
36	Resource I & Fiber	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.50%/hr
37	Resource I & Fiber	34.7	17.3% Glycerin & 13.2% EB2	34.8	3.13%/hr
38	Resource I & Fiber	38.0	19.0% Glycerin & 5.0% EB2	38.0	3.33%/hr
39	Resource I & Fiber	39.6	20.6% Glycerin	39.8	-
40	Resource I, Fiber, & OB Tampon	34.7	17.3% Glycerin & 13.2% EB2	34.8	0.81%/hr
41	Resource I, Fiber, & OB Tampon	38.0	19.0% Glycerin & 5.0% EB2	38.0	1.07%/hr
42	Reverse Roller, Scale-up Run, Fiber & Polyester Liner	38.1	19.1% Glycerin & 4.7% EB2	38.1	-

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EB2 is Eumulgin B2, which is cetcareth-20 and is available from Henkel Corp. of Hoboken, NJ.

The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc.,
5 of Allentown, PA.

Examples 43-46

Water soluble films having the formulations of Table 4 were prepared as described in Examples 1-32. In Examples 43-46, the solution was dried at a temperature of
10 about 60-90° C for less than about 30 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. The substrate for Example 43-46 was polyester.

The time for the dissolution rate to plateau was determined as discussed above.

The results are shown in Table 4 below.

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Table 4

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
43	Resource I	67.2% PVA 52-22	21.7% PEG 400	11.1	20-30
44	Resource I	58.22% PVA 52-22	18.9% PG & 15.7% EB2	7.2	20-30
45	Resource I	34.9% PVA 52-22 and 11.7% PVA 71-30	20.9% PG & 17.5% EB2	15.0	10-15
46	Resource I	46.6% HPMC E50LV	20.9% PG & 17.5% EB2	15.0	5-10

PG is propylene glycol

PEG is polyethylene glycol.

EB2 is Eumulgin B2, which is cetareth-20 and is available from Henkel Corp. of Hoboken, NJ.

PVA is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

HPMC is hydroxypropyl methylcellulose.

Example 47

A water soluble film having the formulation of Table 5 was prepared as follows. Glycerin and nonoxynol-9 were added into cold water and mixed until uniform. The solution was heated to about 60-80° C and the film former, i.e., polyvinyl alcohol, was added under constant mixing. The solution was mixed, deaerated, and cooled to about room

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temperature. The solution was coated onto a stainless steel surface with a web thickness of 0.01 to 0.03 cm. The solution was dried in a multi-zone drying tunnel at a temperature of about 60-90° C for less than about 30 minutes to form a film. The film was then cured with moisture at a relative humidity of about 65-90% and at a temperature of about 40-60° C.

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Table 5

Ingredient	% by weight
Polyvinyl Alcohol (5 cps)	66.0
Glycerin	6.0
Nonoxynol-9	28.0

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All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

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What is claimed is:

1. A method of preparing a water soluble film, the method comprising the steps of
 - 5 (a) preparing a solution comprising
 - (i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,
 - (ii) a water soluble plasticizer having at least one of a
 - 10 hydroxyl, amido, or amino group and a boiling point greater than about 150° C,
 - (iii) a pharmaceutically active agent, and
 - (iv) a solvent;
 - (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and
 - 15 (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%.
2. The method of claim 1, wherein the solution has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying.
- 20 3. The method of claim 1, wherein the film former is polyvinyl alcohol.
4. The method of claim 1, wherein the film former is a partially hydrogenated polyvinyl alcohol.
- 25 5. The method of claim 1, wherein the plasticizer is a polyhydroxy compound.

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6. The method of claim 5, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing.

7. The method of claim 1, wherein the pharmaceutically active agent is selected from imidazole antifungal agents, antibacterial agents, antiseptic agents, hormones, anti-inflammatory agents, anesthetics, spermicides, and any combination of any of the foregoing.

8. The method of claim 1, wherein the pharmaceutically active agent is nonoxynol-9.

9. The method of claim 1, wherein the pharmaceutically active agent is miconazole.

10. The method of claim 1, wherein the pharmaceutically active agent is metronidazole.

11. The method of claim 1, wherein the solvent is selected from the group consisting of water, ethanol, glycerin, ethylene glycol, amides, amines, and any combination of any of the foregoing.

12. The method of claim 11, wherein the solvent is water.

13. The method of claim 11, wherein the solvent is a mixture of water and ethanol.

14. The method of claim 1, wherein the solution comprises from about 5 to about 40% by weight of film former, based upon 100% total weight of solution.

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15 The method of claim 14, wherein the solution comprises from about 15
to about 35% by weight of film former, based upon 100% total weight of solution

16 The method of claim 1, wherein the solution comprises from about 0.1
5 to about 10% by weight of plasticizer, based upon 100% total weight of solution

17 The method of claim 16, wherein the solution comprises from about 0.5
to about 5% by weight of plasticizer, based upon 100% total weight of solution

10 18 The method of claim 1, wherein the solution comprises a
pharmaceutically effective amount of pharmaceutically active agent

19 The method of claim 18, wherein the solution comprises from about 1
to about 30% by weight of pharmaceutically active agent, based upon 100% total weight of
15 solution

20 The method of claim 1, wherein the solution comprises from about 20
to about 90% by weight of solvent, based upon 100% total weight of solution

20 21 The method of claim 1, wherein the solution comprises
(a) about 26.4% by weight of polyvinyl alcohol,
(b) about 2.4% by weight of glycerin,
(c) about 11.2% by weight of monoxynol 9, and
(d) about 60% by weight of water,
25 based upon 100% total weight of solution

22 The method of claim 1, wherein the water soluble film further
comprises
(i) a surfactant,
30 (ii) a preservative,

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- (iii) a viscosity enhancer,
- (iv) a colorant,
- (v) a fragrance,
- (vi) a flavorant,
- (vii) a lubricant,
- (viii) a filler,
- (ix) a binder,
- (x) a wetting agent,
- (xi) a penetration agent,
- (xii) a pH adjuster,
- (xiii) a disintegrant,
- (xiv) an excipient, or
- (xv) any combination of any of the foregoing

23 The method of claim 1, wherein the drying step ~~comprises~~

- (i) heating the solution to from about 50 to about 70° C, and
- (ii) heating the ~~solution~~ to from about 70 to about 100° C

24 The method of claim 1, wherein the curing step is performed at a temperature of from about 25 to about 60° C

25 The method of claim 1, wherein the curing step is performed at a relative humidity of at least about 50%

26 The method of claim 1, wherein the curing step is performed at a relative humidity of from about 60 to about 90%

27 The method of claim 1, wherein the water soluble film has a ~~thickness~~ of from about 0.03 to about 0.50 mm

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28. The method of claim 1, wherein step (a) comprises

(i) preparing a solution comprising

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any

5 combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent; and

10 (ii) pouring or casting the solution on a substrate.

29. The method of claim 28, wherein the substrate is cotton or non-woven fiber.

15 30. A water soluble film prepared by the method of claim 1.

31. A dosage unit form having a water soluble film prepared by the method of claim 1.

20 32. A tampon having a water soluble film prepared by the method of claim 1.

33. An applicator having a water soluble film prepared by the method of claim 1.

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ABSTRACT

The present invention provides a method of preparing a water soluble film. The method comprises (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

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DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **METHOD OF PREPARING A WATER SOLUBLE FILM**, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on

Application Serial No.

and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

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Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications) listed below:

60/172.085
(Application Number)

December 23, 1999
(Filing Date)

(Application Number)

(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.

Filing Date

Status

Application Serial No.

Filing Date

Status

002710.8/TT8460

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I hereby appoint the following attorneys) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Audley A. Ciamporcero, Jr. (#26,051), Steven P. Berman (#24,772), Andrea L. Colby (#30,194), Michael Stark (#32,495), Michael Q. Tatlow (#20,501), Gordon D. Coplein (#19,165), William F. Dudine, Jr. (#20,569), Michael J. Sweedler (#19,937), S. Peter Ludwig (#20,298), Harold E. Wurst (#22,183), Joseph B. Lerch (#26,936), Melvin C. Garner (#26,272), Ethan Horwitz (#27,464), Beverly B. Goodwin (#28,417), Adda C Gorgoris (#29,714), Martin E. Goldstein (#20,869), Bert J. Lewen (#19,407), Henry Sternberg (#22,408), Robert A. Green (#28,301), Peter C., Schechter (#31,662), Robert Schaffer (#31,194), Robert C. Sullivan (#30,499), Ira J. Levy (#35,587), Joseph R. Robinson (#33,448), Jay P. Lessler (#41,151),

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