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(71) **Applicant**: **AEQUUS PHARMACEUTICALS INC.** [CA/CA]; 2820-200 Granville Street, Vancouver, British Columbia V6C 1S4 (CA).

(72) **Inventors**: **PLAKOGIANNIS, Fotios, M.**; 157-14 Cryders Lane, Whitestone, New York 11357 (US). **HOSSAIN, Muhammed, Anwar**; 17 Quaspeak Road, Congers, New York 10920 (US).

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(54) **Title**: ARIPIPRAZOLE COMPOSITIONS AND METHODS FOR ITS TRANSDERMAL DELIVERY

(57) **Abstract**: The present invention discloses compositions of liquid and gel formulation containing aripiprazole in the form of a patch for transdermal delivery wherein the aripiprazole is present in the amount of 7% w/v, the gel contains a gelling agent in the range of 0.1% to 5% w/v, the compositions further contain dimethylsulfoxide, N-methyl-2-pyrrolidone, alcohol, glycol, fatty acids and/or water as permeation enhancers, and the pH of the compositions are maintained at approximately 6 to 7.

ARIPIPRAZOLE COMPOSITIONS AND METHODS FOR ITS TRANSDERMAL DELIVERY

This international application claims priority under 35 U.S.C. §120 of U.S. Patent Application No. 14/825,318, filed August 13, 2015, which is a continuation-in-part of U.S. Patent Application Serial No. 13/879,485, filed April 15, 2013, which is a National Stage filing of PCT/US2011/057080, filed October 20, 2011, which claims benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 61/407,591, filed October 28, 2010, all of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to the field of transdermal delivery of pharmaceutical compositions, which have an acceptable in vitro performance and good bioavailability. In particular, the transdermal pharmaceutical compositions of the present invention include liquids or gels of aripiprazole in a patch dosage form.

BACKGROUND OF INVENTION

Aripiprazole (ARPZ) is the first of a new class of atypical antipsychotics (third generation). Biochemically, ARPZ is a partial agonist of the D2 family of dopamine receptors.[1,2] It is active against positive and negative symptoms of schizophrenia.[3,4]

ARPZ is a quinolinone derivative, white crystalline powder, practically insoluble in water, with a low melting point (135-140°C), MW 448,38g/mole and partition coefficient of 4.54.

BRIEF SUMMARY OF THE INVENTION

The invention provides a pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, Carbopol about 5%, DMSO about 40%, Ethanol about 25%, Lactic acid about 5%, N-methyl-2-pyrrolidone (NMP) about 1.75%, Oleic acid about 4%, propylene glycol (PG) about 7.25%, and q.s. water. The invention provides a pharmaceutical composition wherein the aripiprazole is in a gel or liquid form. The invention provides a pharmaceutical composition wherein the pH of the composition is approximately 6 to 7.

The invention provides a pharmaceutical composition pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, Klucel (hydroxypropylcellulose (HPC)) about 2%, DMSO about 40%, Ethanol about 25%, Lactic acid about 5%, N-methyl-2-pyrrolidone (NMP) about 1.75%, Oleic acid about 4%, propylene glycol about 10.25%, and q.s. water. The invention provides a pharmaceutical composition wherein the aripiprazole is in a gel or liquid form. The invention provides a pharmaceutical composition wherein the pH of the composition is approximately 6 to 7.

The invention provides a pharmaceutical composition pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising about aripiprazole about 7%, Klucel (hydroxypropylcellulose (HPC)) about 4%, DMSO about 5%, Ethanol about 5%, isopropyl myristate (IPM) about 1.5%, Oleic acid about 23%, Lactic acid about 6%, PG about 23.5%, Polyethylene glycol (PEG) - 20%, and Glycerin about 5%. The invention provides a pharmaceutical composition wherein the aripiprazole is in a gel or liquid form. The invention provides a pharmaceutical composition wherein the pH of the composition is approximately 6 to 7.

The invention provides a pharmaceutical composition pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising about aripiprazole about 7%, DMSO about 40%, N-methyl-2-pyrrolidone (NMP) about 1.75%, propylene glycol (PG) - 10.25%, Ethanol about 16%, Lactic acid about 5%, Terpineol about 10%, Oleic acid about 2%, Water about 5%, and Carbopol about 3%. The invention provides a pharmaceutical composition wherein the aripiprazole is in a gel or liquid form. The invention provides a pharmaceutical composition wherein the pH of the composition is approximately 6 to 7.

The invention provides a pharmaceutical composition pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, DMSO about 40%, N-methyl-2-pyrrolidone (NMP) about 1.75%, propylene glycol (PG) about 9.25%, Ethanol about 25%, Lactic acid about 5%, Oleyl alcohol about 4%, Water about 5%, and Carbopol about 3%. The invention provides a pharmaceutical composition wherein the aripiprazole

is in a gel or liquid form. The invention provides a pharmaceutical composition wherein the pH of the composition is approximately 6 to 7.

The invention provides a method of treating schizophrenia in patient in need of such treatment comprising: selecting a patient in need of treatment for schizophrenia; administering the pharmaceutical composition of the invention, thereby treating schizophrenia. The invention provides for the use of a pharmaceutical composition of the invention to manufacture a medicament for treating, for example, schizophrenia.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

The invention will be described in conjunction with the following drawings wherein:

Figure 1 is a chart showing the Effect of Drug Concentration on the Flux of ARPZ through Cellulose Membrane from 0.5% Carbopol 971 Gel Systems.

Figure 2 is a chart showing the Cumulative Amount of 5% ARPZ Permeated through Cadaver Skin from 0.5% Carbopol Gel System.

Figure 3 is a chart showing the Cumulative Amount of Drug Permeated through Human Cadaver Skin from 5% ARPZ in 0.5% Carbopol Gel Systems with Enhancers (Fatty Acids).

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is an elderly human. In another embodiment, the subject is a human adult. In another embodiment, the subject is a human child. In yet another embodiment, the subject is a human infant.

As used herein, the term "agent" refers to any molecule, compound, methodology and/or substance for use in the prevention, treatment, management and/or diagnosis of a disease or condition. As used herein, the term "effective amount" refers to the amount of a therapy that is sufficient to result in the prevention of the development, recurrence, or onset of a disease or condition, and one or more symptoms thereof, to enhance or improve the prophylactic effect(s) of another

therapy, reduce the severity, the duration of a disease or condition, ameliorate one or more symptoms of a disease or condition, prevent the advancement of a disease or condition, cause regression of a disease or condition, and/or enhance or improve the therapeutic effect(s) of another therapy.

As used herein, the phrase "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia, or other generally recognized pharmacopeia for use in animals, and more particularly, in humans.

As used herein, the term "therapeutic agent" refers to any molecule, compound, and/or substance that is used for the purpose of treating and/or managing a disease or disorder.

As used herein, the terms "therapies" and "therapy" can refer to any method(s), composition(s), and/or agent(s) that can be used in the prevention, treatment and/or management of a disease or condition, or one or more symptoms thereof. In certain embodiments, the terms "therapy" and "therapies" refer to small molecule therapy.

As used herein, the terms "treat," "treatment," and "treating" in the context of the administration of a therapy to a subject refer to the reduction or inhibition of the progression and/or duration of a disease or condition, the reduction or amelioration of the severity of a disease or condition, such as cancer, and/or the amelioration of one or more symptoms thereof resulting from the administration of one or more therapies.

The term "derivative" or "derivatized" as used herein includes chemical modification of a compound of the invention, or pharmaceutically acceptable salts thereof or mixtures thereof. That is, a "derivative" may be a functional equivalent of a compound of the invention, which is capable of inducing the improved pharmacological functional activity in a given subject. Illustrative of such chemical modifications would be replacement of hydrogen by a halo group, an alkyl group, an acyl group or an amino group.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts or addition salts of free bases. The term "pharmaceutically acceptable salts" of a compound of the invention is also meant to include within its scope all the possible isomers and their mixtures, and any pharmaceutically acceptable metabolite, bioprecursor and/or pro-drug, such as, for example, a compound which

has a structural formula different from the one of the compounds of the invention, and yet is directly or indirectly converted in vivo into a compound of the invention, upon administration to a subject, such as a mammal, particularly a human being.

The compound may be in the form of a pharmaceutically acceptable salt, such as an acid addition salt or a base salt, or a solvate thereof, including a hydrate thereof. Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts. Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

The invention provides a pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery. The invention provides a pharmaceutical composition of the invention wherein the aripiprazole is in a gel or liquid form. The invention provides a pharmaceutical composition of the invention wherein the aripiprazole is present in the amount of 1 to 20% w/v. The invention provides a pharmaceutical composition of the invention wherein the aripiprazole is present in the amount of 1 to 20% w/v. The invention provides a pharmaceutical composition of the invention wherein the gel contains a gelling agent in the range of about 0.1% to 5% w/v. The invention provides a pharmaceutical composition of the invention further comprising approximately 40% N-methyl-2-pyrrolidone, 40% Dimethylsulfoxide, 15% alcohol and 5% water.

The invention provides a pharmaceutical composition for transdermal delivery which comprises ARPZ 2%; DMSO at a concentration of about 10 to 40%, and at a preferred concentration of about 25%; NMP at a concentration of about 5 to 40%, and a preferred concentration is about 10%; Isopropyl alcohol (IPA) at a concentration of about 1 to 15% , and a preferred concentration is about 5%; Ethyl Alcohol at a concentration of about 15 to 40%, and a preferred concentration is about 40%; PEG 400 at a concentration of about 1 to 15%, and a preferred concentration is about 15%; CARBOPOL® 971P at a concentration of about 0.25 to 5%, and a preferred concentration is about 0.5%; and water, q.s. to 100%.

The invention provides a pharmaceutical composition of the invention being in the form of a liquid and comprising an alcohol, glycol, mineral oil, and/or vegetable oil. The invention provides a pharmaceutical composition of the invention wherein the composition is in a gel form and further comprises a gelling agent selected from the group consisting of natural polymers, semisynthetic polymers, synthetic polymers, carboxyvinyl polymers or carbomers, CARBOPOL® 940, CARBOPOL® 934, CARBOPOL® 971, poloxamer, polyacrylamide, polyvinyl alcohol, polyethylene and co-polymers thereof. The invention provides a pharmaceutical composition of the invention wherein the form is a patch for transdermal delivery. The invention provides a pharmaceutical composition of the invention being in the dosage form of an ointment, cream, emulsion, or liposome. The invention provides a pharmaceutical composition of the invention wherein the aripiprazole is present in the amount of 1 to 20% w/v.

The invention provides a pharmaceutical composition of the invention further comprising an enhancer. The invention provides a pharmaceutical composition of the invention wherein the enhancer is selected from the group consisting of lauric acid, myriste acid, water, sulfoxides, dimethylsulfoxide, dimethylacetamide, dimethylformamide, decymethylsulfoxide, pyrrolidones, fatty acid esters, fatty acids, alcohols, fatty alcohols and glycols, urea, essential oils, terpene and terpenoids, liposomes, niosomes, transferomes and ethanosomes.

The invention provides a pharmaceutical composition of the invention wherein the pH of the composition is maintained at approximately 6 to 7. The invention provides a pharmaceutical composition of the invention wherein the pH of the composition is maintained at approximately 6 to 7.

In an exemplary embodiment, the invention provides a pharmaceutical composition comprising about ARPZ - 7%, Carbopol - 5%, DMSO - 40%, Ethanol - 25%, Lactic acid - 5%, N-methyl-2-pyrrolidone (NMP) - 1.75%, Oleic acid - 4%, propylene glycol (PG) - 7.25%, and q.s. Water (ca. 5%).

In an exemplary embodiment, the invention provides a pharmaceutical composition comprising about ARPZ - 7%, Klucel (hydroxypropylcellulose (HPC)) - 2%, DMSO - 40%, Ethanol - 25%, Lactic acid - 5%, N-methyl-2-pyrrolidone (NMP) - 1.75%, Oleic acid - 4%, propylene glycol - 10.25%, and q.s. Water (ca. 5%).

In an exemplary embodiment, the invention provides a pharmaceutical composition comprising about ARPZ - 7%, Klucel (hydroxypropylcellulose (HPC)) - 4%, DMSO - 5%, Ethanol - 5%, isopropyl myristate (IPM) - 1.5%, Oleic acid - 23%, Lactic acid - 6%, PG - 23.5%, Polyethylene glycol (PEG) - 20%, and Glycerin- 5%.

In an exemplary embodiment, the invention provides a pharmaceutical composition comprising about ARPZ - 7%, DMSO - 40%, N-methyl-2-pyrrolidone (NMP) - 1.75%, propylene glycol (PG) - 10.25%, Ethanol - 16%, Lactic acid - 5%, Terpineol - 10%, Oleic acid - 2%, Water - 5%, and Carbopol - 3%.

In an exemplary embodiment, the invention provides a pharmaceutical composition comprising about ARPZ - 7%, DMSO - 40%, N-methyl-2-pyrrolidone (NMP) - 1.75%, propylene glycol (PG) - 9.25%, Ethanol - 25%, Lactic acid - 5%, Oleyl alcohol - 4%, Water - 5%, and Carbopol - 3%.

Preparation of suitable formulations is within the skill of those in the art, and suitable excipients for inclusion in any such formulation include, for example, gellants, viscosifiers, penetration enhancers, preservatives, such as antibiotics and antifungals, and cosmetic ingredients, such as scents and colorings.

Suitable preservatives will be apparent to those skilled in the art, and include the parabens (methyl, ethyl, propyl and butyl), benzoic acid and benzyl alcohol. Preservatives employed solely for that purpose will generally form 1% (w/w) or less of the final topical formulation.

Pharmaceutical compositions of the present invention can include nanoparticles, composite nanoparticles, nanosuspension, or nanocapsules of the present invention

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

ARPZ is practically insoluble in water and has been formulated as a liquid and gel dosage form (Table 1). All reported values are in weight/volume percentage (W/V)

TABLE 1: Composition of liquid and gel formulation of Aripiprazole (5% W/V)

	W/V	W/V
N-methyl-2-pyrolidone (NMP)	40 %	40 %
Dimethyl Sulfoxide (DMSO)	40 %	40%
Ethyl Alcohol	15 %	15%
Carbopol 971P		0.5 %
Water	5 %	4.5%
Total	100.00 %	100.00%

An optimal mixture design of experiments was used to select the levels of the formulation variables. The optimum composition of a 1% W/V to 20% W/V ARPZ liquid formulation was predicted to have NMP 40%, DMSO 40%, Alcohol 15% and water 5% (Table 1). The gel formulation should contain a gelling agent in the range of about 0.1% to 5% W/V and the optimum APRZ composition should range from about 1% W/V to 20% W/V with about .5% W/V of the gelling agent. Therefore, the gel formulation was predicted to have a NMP of 40%, DMSO 40%, Alcohol 15%, Carbopol 971 0.5%, and Water 4.5% (Table 1). However, Table 2 lists other combinations that also could produce successful liquid and gel ARPZ formulations in accordance with the present invention.

TABLE 2. Concentration Ranges of N-Methyl-2-Pyrolidone (NMP), Dimethl Sulfoxide (DMSO), Ethyl Alcohol, and Water in Liquid Aripiprazole Formulation

Formulation	NMP	DMSO	Alcohol	Water
1.	50	50	---	-----
2.	40	40	20	-----
3.	40	40	-----	20
4.	40	40	15	5
5.	40	40	10	10
6.	40	40	5	15
7.	30	30	20	20
8.	30	30	30	10

9.	30	40	25	5
10.	40	30	25	5
11.	45	45	10	0
12.	45	40	10	5

Other than these components, other solvents known to those skilled in the art suitable for use in the present invention can be used to prepare the liquid formulation, and combinations thereof, including but not limited to alcohols such as but not limited to (methyl, ethyl, butyl, propyl, isopropyl, isopropyl myristate, etc.), glycols such as, but not limited to (propylene, polyethylene, glycerin, etc.) mineral oils, vegetable oils, and others.

Example 2

The effect of gelling agents and their concentration on the permeation of ARPZ through artificial membranes and human cadaver skin was evaluated and two characteristic graphs are shown in Figures 1 & 2. The optimal desired composition of ARPZ gel formulation contains 0.5% W/V Carbopol 971. ARPZ can be gelled by gelling agents, including but not limited to, natural polymers (such as agar, alginic acid and derivatives, cassia tora, collagen, gelatin, gellum gum, guar gum, pectin, potassium, or sodium carageenan, tragacanth, xanthan, etc), semisynthetic polymers (such as methylcellulose, carbosymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, etc.) synthetic polymers (such as carboxyvinyl polymers or carbomers: carbopol 940, carbopol 934, carbopol 971, poloxamer, polyacrylamide, polyvinyl alcohol, polyethylene, and its co-polymers etc), and clays (such as silicates, etc). In addition, other than cellulose membranes, ARPZ can be evaluated with other artificial membranes including but not limited to silicone membranes (polydimethylsiloxane), liposome-coated membranes, solid-supported liquid membranes, lecithin organogel membranes and others. Besides the gel formulations of ARPZ, other dosage forms include, but are not limited to, ointments, creams, emulsions, liposomes, etc. may be used.

Example 3

The effect of enhancers on the flux of ARPZ through human cadaver skin was evaluated and is shown in Figure 3. The desired optimum composition of ARPZ gel formulation contained Lauric and Myristc acid. Apart from Lauric and Myristc

acid enhancer, the ARPZ transdermal delivery can be influenced by enhancers including but not limited to water, sulfoxides, and similar chemicals, dimethylsulfoxide (DMSO), dimethylacetamide (DMAC), dimethylformamide (DMF), decymethylsulfoxide (DCMS) etc, azone, pyrrolidones N-methyl-2-pyrrolidone (NMP), 2-pyrrolidon (2p), etc., fatty acids esters (butyl ethanoate, ethyl ethanoate, ethyl oleate, isopropyl myristate, isopropyl palmiate, methyl ethanolate, etc.), fatty acids (capric, caprylic, lauric, oleic, myristic, linoleic, stearic, palmitic etc), alcohols, fatty alcohols and glycols (nathanol, dodecanol, propylene glycols, glycerol etc), urea, essential oils, terpene and terpenoids (limonene, thymol, cineole etc), liposomes, niosomes, transferomes, ethanosomes, etc.

Example 4

The effects of pH on the permeation of ARPZ through human cadaver skin were evaluated and a characteristic graph is shown in Figure 2. The preferred optimum composition of ARPZ gel transdermal formulation had a pH in the range of approximately 6 to 7. Other than these optimal pH values, the ARPZ transdermal delivery may be influenced by pH values outside of the preferred range, but to a lesser extent. Thus, the present invention may still be achieved outside of the preferred pH range of approximately 6 to7, depending upon the circumstances of use.

The systems of this discovery can deliver ARPZ at a flux between 50mcg/ch-2.h and 800mcg/ch-2.h, which can produce the required therapeutic ARPZ blood levels. Flux rate can be changed by modifying such parameters as ARPZ initial concentration, surface area of the patch, pH of the formulation, vehicle composition, enhancer type and composition, etc., in accordance with the teachings of the present invention.

Optimum therapeutic outcome requires not only a proper drug selection but also an effective drug delivery. Psychotropic drug compliance of rigorous regular medication schedules is of great importance. In many instances, oral administration of psychotropic agents is considered a less than optimal delivery system due to patient non-compliance[5]. Transdermal delivery of psychotropic drugs, especially with prolonged duration of action, would be valuable in increasing medication compliance, especially in the geriatric population. Further, potential advantages of ARPZ transdermal delivery are as follows: lack of hepatic first pass effect;

eliminating the potential for over- or under- dosing; allowing the flexibility of terminating the drug administration by simply removing the patch; providing a simplified therapeutic regimen, thereby assisting medication compliance in the geriatric population.

Example 5

A transdermal composition of Aripiprazole is shown below:

ARPZ	2 %
DMSO	25%
NMP	10%
Isopropylalcohol (IPA)	5%
Ethyl Alcohol	40%
PEG 400	15%
Carbopol 971P	0.5%
HCl	q.s. to pH 6-7
WATER	q.s. to 100%

Example 6

A transdermal composition of Aripiprazole is shown below:

ARPZ	7%
Carbopol	5%
DMSO	40%
Ethanol	25%
Lactic acid	5%
NMP	1.75%
Oleic acid	4%
PG	7.25%
Water	5%

Example 7

A transdermal composition of Aripiprazole is shown below:

ARPZ	7%
Klucel	2%

DMSO	40%
Ethanol	25%
Lactic acid	5%
NMP	1.75%
Oleic acid	4%
PG	10.25%
Water	5%

Example 8

A transdermal composition of Aripiprazole is shown below:

ARPZ	7%
Klucel	4%
DMSO	5%
Ethanol	5%
IPM	1.5%
Oleic acid	23%
Lactic acid	6%
PG	23.5%
PEG	20%
Glycerin	5%

Example 9

A transdermal composition of Aripiprazole is shown below:

ARPZ	7%
DMSO	40%
NMP	1.75%
PG	10.25%
Ethanol	16%
Lactic acid	5%
Terpineol	10%
Oleic acid	2%
Water	5%

Carbopol	3%

Example 10

A transdermal composition of Aripiprazole is shown below:

ARPZ	7%
DMSO	40%
NMP	1.75%
PG	9.25%
Ethanol	25%
Lactic acid	5%
Oleyl alcohol	4%
Water	5%
Carbopol	3%

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, Carbopol about 5%, DMSO about 40%, Ethanol about 25%, Lactic acid about 5%, N-methyl-2-pyrrolidone (NMP) about 1.75%, Oleic acid about 4%, propylene glycol (PG) about 7.25%, and q.s. water.

2. The pharmaceutical composition of claim 1 wherein the aripiprazole is in a gel or liquid form.

3. The pharmaceutical composition of any one of claims 1 - 2 wherein the pH of the composition is approximately 6 to 7.

4. A pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, Klucel (hydroxypropylcellulose (HPC)) about 2%, DMSO about 40%, Ethanol about 25%, Lactic acid about 5%, N-methyl-2-pyrrolidone (NMP) about 1.75%, Oleic acid about 4%, propylene glycol about 10.25%, and q.s. water.

5. The pharmaceutical composition of claim 4 wherein the aripiprazole is in a gel or liquid form.

6. The pharmaceutical composition of any one of claims 4 - 5 wherein the pH of the composition is approximately 6 to 7.

7. A pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising about aripiprazole about 7%, Klucel (hydroxypropylcellulose (HPC)) about 4%, DMSO about 5%, Ethanol about 5%, isopropyl myristate (IPM) about 1.5%, Oleic acid about 23%, Lactic acid about 6%, PG about 23.5%, Polyethylene glycol (PEG) - 20%, and Glycerin about 5%.

8. The pharmaceutical composition of claim 7 wherein the aripirazole is in a gel or liquid form.

9. The pharmaceutical composition of any one of claims 7 - 8 wherein the pH of the composition is approximately 6 to 7.

10. A pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising about aripiprazole about 7%, DMSO about 40%, N-methyl-2-pyrrolidone (NMP) about 1.75%, propylene glycol (PG) - 10.25%,

Ethanol about 16%, Lactic acid about 5%, Terpineol about 10%, Oleic acid about 2%, Water about 5%, and Carbopol about 3%.

11. The pharmaceutical composition of claim 10 wherein the aripiprazole is in a gel or liquid form.

12. The pharmaceutical composition of any one of claims 10 - 11 wherein the pH of the composition is approximately 6 to 7.

13. A pharmaceutical composition comprising aripiprazole in a dosage form for transdermal delivery comprising aripiprazole about 7%, DMSO about 40%, N-methyl-2-pyrrolidone (NMP) about 1.75%, propylene glycol (PG) about 9.25%, Ethanol about 25%, Lactic acid about 5%, Oleyl alcohol about 4%, Water about 5%, and Carbopol about 3%.

14. The pharmaceutical composition of claim 13 wherein the aripiprazole is in a gel or liquid form.

15. The pharmaceutical composition of any one of claims 13 - 14 wherein the pH of the composition is approximately 6 to 7.

16. A method of treating schizophrenia in patient in need of such treatment comprising:

- selecting a patient in need of treatment for schizophrenia;
- administering the pharmaceutical composition of any one of claims 1 - 15, thereby treating schizophrenia.

Figure 1

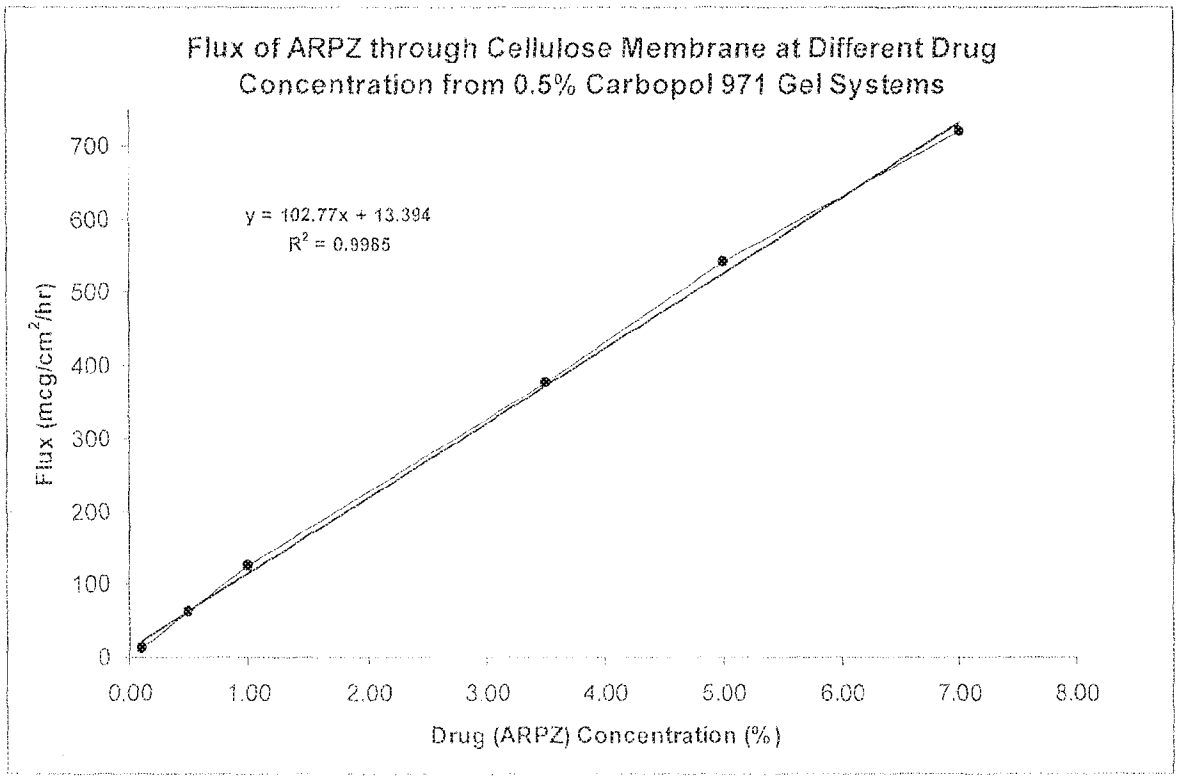

Flux of ARPZ through Cellulose Membrane at Different Drug Concentration from 0.5% Carbopol 971 Gel Systems
y = 102.77x + 13.394
R² = 0.9985
Flux (mcg/cm²/hr)
0
100
200
300
400
500
600
700
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
Drug (ARPZ) Concentration (%)

Figure 2

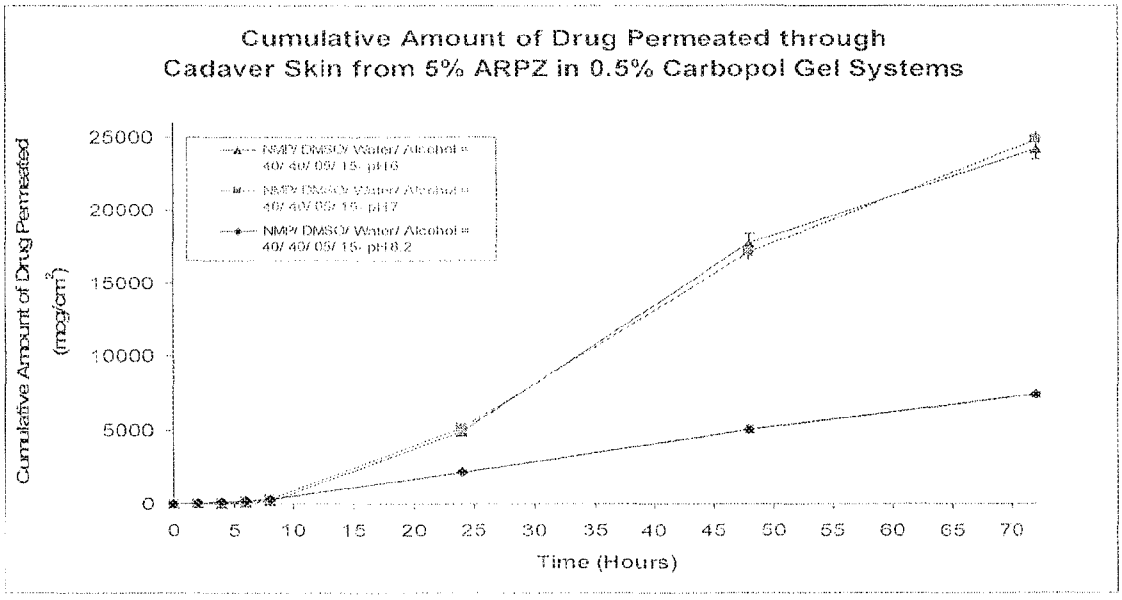
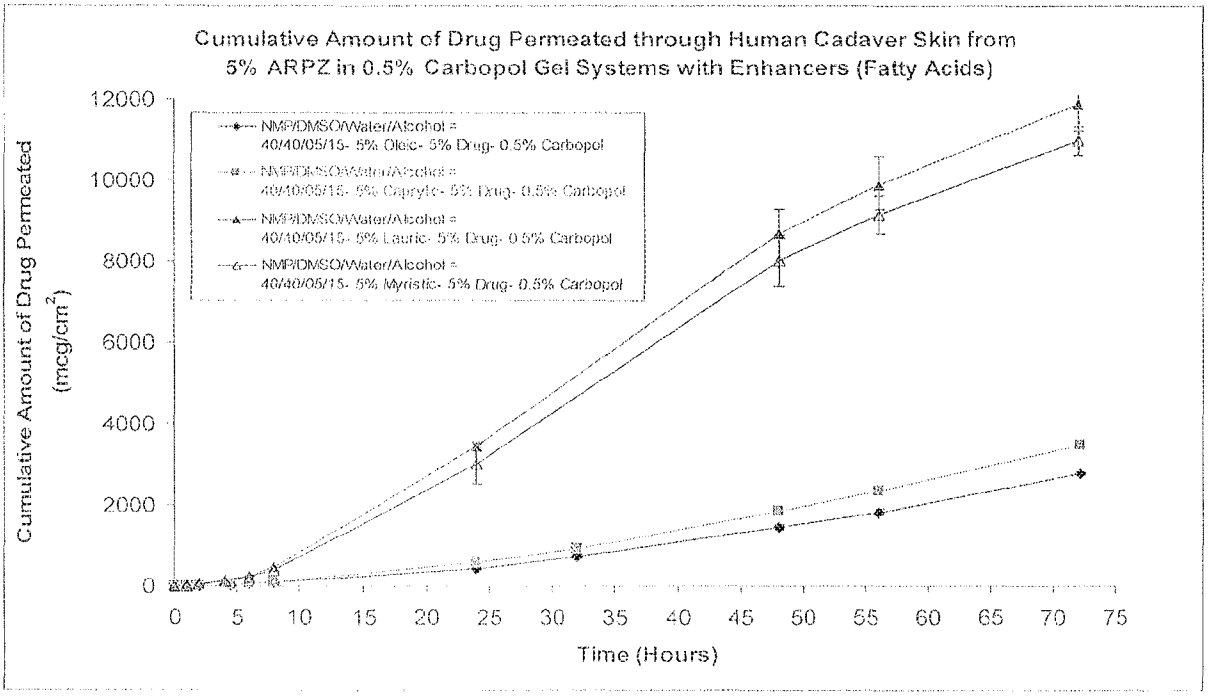

Cumulative Amount of Drug Permeated through
Cadaver Skin from 5% ARPZ in 0.5% Carbopol Gel Systems
Cumulative Amount of Drug Permeated (mcg/cm²)
25000
20000
15000
10000
5000
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70
Time (Hours)
NMP/ DMSO/ Water/ Alcohol = 40/ 40/ 05/ 15- pH8.2

Figure 3


Cumulative Amount of Drug Permeated through Human Cadaver Skin from 5% ARPZ in 0.5% Carbopol Gel Systems with Enhancers (Fatty Acids)
Cumulative Amount of Drug Permeated (mcg/cm²)
Time (Hours)
NMP/DMSO/Water/Alcohol = 40/40/05/15- 5% Oleic- 5% Drug- 0.5% Carbopol
NMP/DMSO/Water/Alcohol = 40/40/05/15- 5% Caprylic- 5% Drug- 0.5% Carbopol
NMP/DMSO/Water/Alcohol = 40/40/05/15- 5% Lauric- 5% Drug- 0.5% Carbopol
NMP/DMSO/Water/Alcohol = 40/40/05/15- 5% Myristic- 5% Drug- 0.5% Carbopol
0
2000
4000
6000
8000
10000
12000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/054826

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/4704*** (2006.01), ***A61K 31/4709*** (2006.01), ***A61K 9/08*** (2006.01), ***A61K 9/10*** (2006.01), ***A61P 25/18*** (2006.01), ***C07D 215/22*** (2006.01), A61K 31/496 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***A61K 31/*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

QUESTEL (FAMPAT: Inventor search; aripiprazole, transdermal) and Canadian Intellectual Property Office Patent Database (classification search; aripiprazole, transdermal)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2,816,203 A1 (PLAKOGIANNIS et al.) 3 May 2012 (03-05-2012) See the whole document.	1-16
A	US 2012/0184563 A1 (HANMA) 19 July 2012 (19-07-2012) See the whole document.	1-16
A	US 2004/0170672 A1 (SELZER) 2 September 2004 (02-09-2004) See the whole document.	1-16

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search 23 November 2016 (23-11-2016)	Date of mailing of the international search report 28 November 2016 (28-11-2016)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Lu Jiang (819) 639-4540

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/054826

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claim Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 16 is directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under PCT Rule 39.1(iv). However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 16.

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		AU2011320758B2	24 September 2015 (24-09-2015)
		BR112013010190A2	13 September 2016 (13-09-2016)
		CN103491961A	01 January 2014 (01-01-2014)
		EP2632463A2	04 September 2013 (04-09-2013)
		EP2632463A4	20 April 2016 (20-04-2016)
		JP2014503479A	13 February 2014 (13-02-2014)
		JP5966228B2	10 August 2016 (10-08-2016)
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		MX2013004693A	01 November 2013 (01-11-2013)
		MX339196B	16 May 2016 (16-05-2016)
		RU2013124401A	10 December 2014 (10-12-2014)
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		US9138402B2	22 September 2015 (22-09-2015)
		US2013171237A1	04 July 2013 (04-07-2013)
		US2015342949A1	03 December 2015 (03-12-2015)
		WO2012058091A2	03 May 2012 (03-05-2012)
		WO2012058091A3	17 October 2013 (17-10-2013)
US2012184563A1	19 July 2012 (19-07-2012)	US8815261B2	26 August 2014 (26-08-2014)
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		WO2010146872A1	23 December 2010 (23-12-2010)
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		DE50208253D1	09 November 2006 (09-11-2006)
		EP1368008A1	10 December 2003 (10-12-2003)
		EP1368008B1	27 September 2006 (27-09-2006)
		ES2274023T3	16 May 2007 (16-05-2007)
		JP2004529891A	30 September 2004 (30-09-2004)
		JP2009173679A	06 August 2009 (06-08-2009)
		WO02069941A1	12 September 2002 (12-09-2002)