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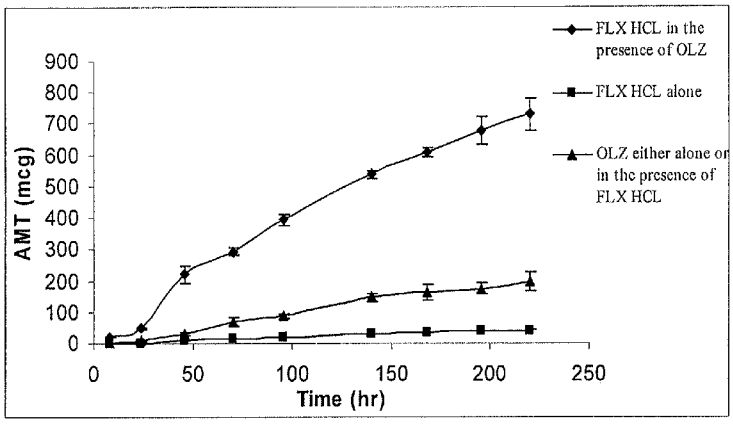
Figure 4



(57) Abstract: The present invention relates to the field of transdermal delivery of pharmaceutical compositions, which have acceptable in vitro performance and good bioavailability. In particular the transdermal pharmaceutical compositions of the present invention in liquid and gel formulations, for example, Fluoxetine (FLX) HCl and Olanzapine (OLZ) in a transdermal patch dosage form, alone and in combination with each other. In addition, describes a new lipophilic penetration enhancer (Olanzapine), which helps the hydrophilic molecules (Fluoxetine HCl) to penetrate though the skin more efficiently than alone.

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PHARMACEUTICAL COMPOSITIONS

SPECIFICATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This PCT application claims the benefit under 35 U.S.C. §119(e) of United States Patent Application Serial No. 61/812,451, filed April 16, 2013, entitled PHARMACEUTICAL COMPOSITIONS, the disclosure of which is incorporated by reference herein.

1. FIELD OF INVENTION

The present invention relates to the field of transdermal delivery of pharmaceutical compositions, which have acceptable in vitro performance and good bioavailability. In particular the transdermal pharmaceutical compositions of the present invention liquids or gels of, for example, Fluoxetine (FLX) HCl and Olanzapine (OLZ) in a patch dosage form. In addition, describes a new lipophilic penetration enhancer (Olanzapine), which helps the hydrophilic molecules (Fluoxetine HCl) to penetrate though the skin more efficiently than alone.

2. BACKGROUND

Fluoxetine HCL also known by the trade name Prozac®, is an antidepressant used for major depressive disorder, obsessive compulsive disorder, bulimia nervosa, panic disorder, and premenstrual dysphoric disorder. Its molecular weight is 345.79 g/mol, pKa is 8.7, log Kow is 1.8 and its solubility in water is 14 mg/ml.

Olanzapine also known by the trade name Zyprexa®, is an atypical antipsychotic agent used to treat both negative and positive symptoms of schizophrenia, acute mania with bipolar disorder, agitation, and psychotic symptoms in dementia. Olanzapine belongs to the thienobenzodiazepine class. Its molecular weight is 312.44 g/mol, log Pow at pH 5,7, and 9 was determined to be 0.3; 1.7; and 2.1 respectively. pKa is 7.34, 4.69, and it is practically insoluble in water.

The combination therapy of FLX and OLZ was found to be a good choice for effective treatment of resistant patients. This combination therapy is providing sufficient improvements in reducing depressive symptoms, than either drug alone. This combination product is available on the market in oral dosage form and is known as SYMBYAX®. However it has some disadvantages, such as low bioavailability, patient non-compliance, failure of taking prescribed doses for those patients with depression, etc.

The compositions of the invention overcome the deficiencies of prior formulations by providing transdermal delivery of pharmaceutical compositions, which have acceptable in vitro

performance and good bioavailability. In particular, the transdermal pharmaceutical compositions of the present invention provide, for example, liquids or gels of Fluoxetine (FLX) HCl and Olanzapine (OLZ) in a patch dosage form. In addition, the invention describes a new lipophilic penetration enhancer (Olanzapine), which helps, for example, the hydrophilic molecules (Fluoxetine HCl) to penetrate though the skin more efficiently than alone.

All references cited herein are incorporated herein by reference in their entireties.

BRIEF SUMMARY OF THE INVENTION

The invention provides a pharmaceutical composition comprising fluoxetine in a dosage form for transdermal delivery, wherein the composition is in gel form, comprising: fluoxetine in the amount of about 0.1% to 40% w/v; optionally, an enhancer selected from the group consisting of olanzapine, clozapine, amoxapine, 2-chlororphenothiazine, piperazine, 1-methylpiperazine, and combinations thereof; and a gelling agent in the range of about 0.1% to 5% w/v.

The invention provides a pharmaceutical composition wherein the enhancer is present at a concentration of about 0.1% to 25% w/v. The invention provides a pharmaceutical composition wherein the enhancer is olanzapine present at a concentration of about 0.1% to 25% w/v. The invention provides a pharmaceutical composition wherein the gelling agent is hydroxypropylcellulose. The invention provides a pharmaceutical composition wherein the form is a patch for transdermal delivery. The invention provides a pharmaceutical composition wherein the dosage form is an ointment, cream, emulsion, or liposome. The invention provides a pharmaceutical composition further comprising about PEG, ethanol, water, and hydroxypropylcellulose. The invention provides a pharmaceutical composition urther comprising about 25% PEG, about 35% ethanol, about 0.5% hydroxypropylcellulose, and q.s. water.

The invention provides a pharmaceutical composition comprising fluoxetine in a dosage form for transdermal delivery, wherein the composition is in liquid form, comprising: fluoxetine in the amount of about 0.1% to 40% w/v; optionally, an enhancer selected from the group consisting of olanzapine, clozapine, amoxapine, piperazine, 1-methylpiperazine, and combinations thereof. The invention provides a pharmaceutical composition wherein the enhancer is present at a concentration of about 0.1% to 25% w/v. The invention provides a pharmaceutical composition wherein the dosage form is a patch for transdermal delivery. The invention provides a pharmaceutical composition further comprising about PEG, ethanol, and

water. The invention provides a pharmaceutical composition further comprising about 25% PEG, about 35% ethanol, and q.s. water.

The invention provides a pharmaceutical composition comprising olanzapine in a dosage form for transdermal delivery, wherein the composition is in gel form, comprising: olanzapine in the amount of about 0.1% to 25% w/v; and a gelling agent in the range of about 0.1% to 5% w/v.

The invention provides a pharmaceutical composition wherein the gelling agent is hydroxypropylcellulose. The invention provides a pharmaceutical composition further comprising about PEG, Ethanol, and water. The invention provides a pharmaceutical composition further comprising about 25% PEG, about 35% ethanol, and q.s. water. The invention provides a pharmaceutical composition wherein the dosage form is a patch for transdermal delivery. The invention provides a pharmaceutical composition being in the dosage form of an ointment, cream, emulsion, or liposome.

The invention provides a pharmaceutical composition comprising olanzapine in a dosage form for transdermal delivery, wherein the composition is in liquid form, comprising: olanzapine in the amount of about 0.1% to 25% w/v. The invention provides a pharmaceutical composition further comprising PEG, ethanol, and water. The invention provides a pharmaceutical composition wherein the dosage form is a patch for transdermal delivery. The invention provides a pharmaceutical composition further comprising about 25% PEG, about 35% ethanol, and q.s. water.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

The invention will be described in conjunction with the following drawings in which like reference numerals designate like elements and wherein:

Fig. 1 is a graph showing Release of Olanzapine (0.1%) alone from Klucel gel formulation (0.5%) through cellulose membrane.

Fig. 2 is a graph showing Release of Fluoxetine HCl (0.1%) alone from Klucel gel formulation (0.5%) through cellulose membrane.

Fig. 3 is a graph showing Simultaneous Release of Fluoxetine HCl (0.1%) and Olanzapine (0.1%) from Klucel gel formulation (0.5%) through cellulose membrane.

Fig. 4 is a graph showing Release profiles of OLZ (0.1%) alone or in the presence of FLX HCl (0.1%), and FLX HCl (0.1%) alone or in the presence of Olanzapine through the human cadaver skin.

Fig. 5 is a graph showing Release of FLX HCl (0.1%) control and released from Klucel® (0.5%) through cadaver skin, which was previously in contact with Olanzapine.

Fig. 6 is a graph showing Release of FLX HCl (0.1%) in the presence of different concentrations of Olanzapine

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention provide transdermal delivery of pharmaceutical compositions, which have acceptable in vitro performance and good bioavailability. In particular, the transdermal pharmaceutical compositions of the present invention provide, for example, liquids or gels of Fluoxetine (FLX) HCl and Olanzapine (OLZ) in a patch dosage form. In addition, the invention describes a new lipophilic penetration enhancer (Olanzapine), which helps, for example, the hydrophilic molecules (Fluoxetine HCl) to penetrate though the skin more efficiently than alone.

Topical Formulations

The term "topical" as employed herein relates to the use of a compound, derivative or analogue as described herein, incorporated in a suitable pharmaceutical carrier, and applied at the site for exertion of local action. Accordingly, such topical compositions including those forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional forms for this purpose include ointments, liniments, creams, lotions, pastes, jellies, sprays, aerosols, soaps, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

For topical use, the agent of the invention can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matrices for slow release delivery may also be used. Typically, the dose to be applied is in the range of about 0.1 ng to about 100 mg per day, or about 1 ng to about 10 mg per day, or about 10 ng to about 1 mg per day depending on the formulation. Furthermore, the topical product can be applied topically through the use of a patch or other delivery device. Delivery devices can include, but are not limited to, those that can be heated or cooled, as well as those that utilize iontophoresis or ultrasound.

For instance, the topical product can be applied, for example, by applying a composition in the form of a skin lotion, clear lotion, milky lotion, cream, gel, foam, ointment, paste, emulsion, spray, conditioner, tonic, cosmetic, , or the like which is intended to be left on the skin or other keratinous tissue (*i.e.*, a "leave-on" composition). After applying the composition to the keratinous tissue (*e.g.*, skin), it in one embodiment, it is left on for a period of at least about 15 minutes, or at least about 30 minutes, or at least about 1 hour, or for at least several hours, *e.g.*, up to about 12 hours. In one embodiment, the topical product is left on overnight. In another embodiment, the topical product is left on all day.

Any suitable method can be used to apply the topical product, including but not limited to for example using the palms of the hands and/or fingers or a device or implement. Another approach to ensure a continuous exposure of the keratinous tissue to at least a minimum level of the topical product is to apply the compound by use of a patch applied, e.g., to the face. The patch can be occlusive, semi-occlusive or non-occlusive, and can be adhesive or non-adhesive. The topical product can be contained within the patch or be applied to the skin prior to application of the patch.

The patch can be left on the skin for any suitable period of time. For example, a period of at least about 5 minutes, or at least about 15 minutes, or at least about 30 minutes, or at least about 1 hour, or at night as a form of night therapy, or in another embodiment all day.

Penetration Enhancers

The inventors have found that a variety of different compounds structurally related to OLZ can increase diffusivity of hydrophilic drugs, such as Fluoxetine HCl and Doxepin HCl through human cadaver skin. These compounds included: Clozapine, Amoxapine, 2-Chlorophenothiazine, Piperazine and 1-Methylpiperazine. All of these compounds more or less resemble an analogue of either the whole molecule of OLZ or some part of its chemical structure. All are diarylazepine derivatives and have tricyclic ring, which is differently modified. They all possess the identical enhancement property however 2-Chlorophenothiazine did not demonstrate any enhancement activity due to the lack of the piperazine ring. Moreover the piperazine has the highest enhancement effect among the tested compounds. Also, Amoxapine has a higher enhancement effect than Olanzapine and Clozapine that have the methyl group in the piperazine moiety. Hence it appears that a piperazine ring attached to the tricyclic system is essential for enhancement activity. The transdermal delivery of FLX in the presence of these compounds is shown in Table 3, Example 6.

Formulations

The invention provides a pharmaceutical composition for transdermal delivery which comprises an active ingredient, such as fluoxetine, at a concentration of about 0.1% to about 40%, preferred concentrations are about 0.1%, 0.5%, 1%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5%, 5.5%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 25.5%, 26%, 27%; preferred concentrations of fluoxetine include about 100 mg, 109 mg, 115 mg, 117 mg, 127 mg, 159 mg, 198 mg, and 211 mg; the composition may optionally include a penetration enhancer, for example, olanzapine at a concentration of about 0.1% to 25%, preferred concentrations are about 0.1%, 0.5%, 1%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5%, 5.5%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%; preferred concentration of penetration enhancer include about 0.98 mg, 1.5 mg, 3.34 mg, 3.35 mg, 5.4 mg, 5.5 mg, 11.5 mg, 25.5 mg; Ethyl Alcohol at a concentration of about 35 to about 70%, and preferred concentrations are about 30%, 35%, 40%, and 45%; PEG at a concentration of about 5% to about 65%, and preferred concentrations are about 20%, 25%, 30%, 35%, and 40%; KLUCEL® (hydroxypropylcellulose) at a concentration of about 0.1% to 5% w/v, and preferred concentrations are about 0.1%, 0.2, %, 0.3%. 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, and 1.0%, 2.0%, 3.0%, 4.0%, 5.0%; and water, q.s. to 100%.

In one embodiment, a gel formulation of the invention may contain, for example, 0.5% W/V CARBOPOL® 971. Compositions of the invention 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, carboxymethylcellulose, 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, compositions of the invention can be used with other artificial membranes including but not limited to silicone membranes (polydimethylsiloxane), liposome-coated membranes, solid-supported liquid membranes, lecithin organogel membranes and other. Besides the gel formulations of the invention, other dosage forms including, but not limited to, ointments, creams, emulsions, liposomes, etc. may be used.

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.

EXAMPLES

Example 1

OLZ is practically insoluble in water while FLX has a reported solubility in water of 14 mg/ml and both have been formulated as a liquid and gel dosage form; either alone or in combination with each other.

An optimal mixture design of experiments was used to select the levels of the formulation variables. The optimum composition of 0.1% w/v to 25% w/v of OLZ and 0.1% w/v to 40% w/v of FLX alone or in combination with each other in liquid formulation was predicted to have PEG (5% to 65%), Ethanol (35% to 70%) and water (0% to 50%). The gel formulation may contain, for example, contain a gelling agent, Klucel® (hydroxypropylcellulose) in the range of about 0.1% w/v to 5% w/v. Therefore, the gel formulation was predicted to have PEG 25%, Ethanol 35%, water 40%, and Klucel 0.5%. However Table 1 lists other combinations that also could produce successful liquid and gel OLZ and/or FLX, alone or in combination with each other in accordance with the present invention.

TABLE 1: Composition of liquid and gel formulation of Olanzapine (0.1%) and Fluoxetine HCl (0.1%)

	W/V	W/V	W/V
PEG	25%	24.5%	25%
Ethanol	34.5%	35%	35%
Water	40%	40%	39.5%
Klucel	0.5%	0.5%	0.5%
Total	100%	100.0%	100%

TABLE 2: Concentration Ranges of PEG, Ethanol, and water in liquid and gel formulations of OLZ and FLX alone and in combination with each other

PEG (ML)	ETHANOL (ML)	WATER (ML)	OLZ (MG)	FLX (MG)
15	35	50	0.98	109
25	35	40	1.5	117
35	35	30	3.345	127
45	35	20	5.457	159
55	35	10	11.52	198
65	35	0	25.556	211

Example 2

It is apparent from Figures 1, 2, and 3 that the release of FLX and OLZ from a gel, Klucel 0.5%, through a cellulose membrane either alone or in combination does not influence the release. Whereas the release of FLX in the presence of OLZ through a Human Cadaver Skin increases the release of hydrophilic FLX to about 20x (Figure 4.)

Example 3

The possibility of reversibility effect of OLZ was investigated and is shown in Figure 5. The result of experiment provided that once OLZ was removed from the skin, its enhancement properties vanished away. In fact, we can see from this graph that the amount of FLX, after the skin treatment with OLZ, was less than twice as high as the control sample, while 17 times higher while in direct intact with OLZ. The figure indicates that the enhancement property of OLZ in the human cadaver skin is reversible.

Example 4

The evaluation of concentration dependency studies of OLZ were performed and represented by the Figure 6. The consistent 0.1% concentration of Fluoxetine HCl was tested under four different concentrations of OLZ (0.05%, 0.1%, 1.5%, 2%). As can be seen by this figure the enhancement properties of OLZ is concentration dependent. The permeability of FLX proportionally increasing with increasing concentration of OLZ.

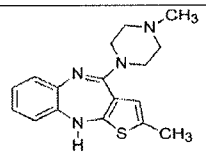
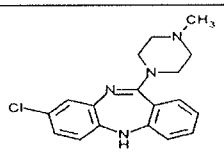
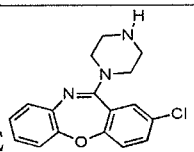
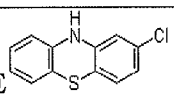
Example 5

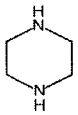
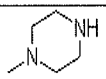
The effect of OLZ on the release of Doxepin HCL from gel (Klucel 0.5%) through Human Cadaver Skin was evaluated and found to be increased by about the same magnitude (20x).

Example 6

To investigate if the whole molecule or some particular group of OLZ is responsible for enhancement property, a variety of different compounds structurally related to OLZ were investigated (Table 3). All of them more or less resemble an analogue of either the whole molecule of OLZ or some part of its chemical structure. These compounds included: Clozapine, Amoxapine, 2-Chlorophenothiazine, Piperazine and 1-Methylpiperazine. The transdermal delivery of FLX in the presence of these compounds is shown in Table 3. All are diarylazepine derivatives and have tricyclic ring, which is differently modified. 2-Chlorophenothiazine did not demonstrate any enhancement activity due to the lack of the piperazine ring. Moreover the piperazine has the highest enhancement effect among the tested compounds. Also, Amoxapine has a higher enhancement effect than Olanzapine and Clozapine that have the methyl group in the piperazine moiety. Hence it appears that a piperazine ring attached to the tricyclic system is essential for enhancement activity.

Table 3. Percent release of FLX HCl in the combination of OLZ and OLZ structurally related compounds

Drugs used in combination with FLX HCL	% Of Release of FLX HCL
FLUOXETINE HCL control	1.33%
OLANZAPINE 	23.4%
CLOZAPINE 	20.6%
AMOXAPINE 	37.5%
2-CHLOROPHENOTHIAZINE 	No effect

PIPERAZINE 	**55.9%**
1-METHYLPIPERAZINE 	**21.3%**

Olanzapine and its structurally related compounds including piperazine can increase diffusivity of hydrophilic drugs, such as Fluoxetine HCl and Doxepin HCl through human cadaver skin, as is shown in Table 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.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising fluoxetine in a dosage form for transdermal delivery, wherein the composition is in gel form, comprising:

- fluoxetine in the amount of about 0.1% to 40% w/v;

- optionally, an enhancer selected from the group consisting of olanzapine, clozapine, amoxapine, 2-chlororphenothiazine, piperazine, 1-methylpiperazine, and combinations thereof; and

- a gelling agent in the range of about 0.1% to 5% w/v.

2. The pharmaceutical composition of claim 1 wherein the enhancer is present at a concentration of about 0.1% to 25% w/v.

3. The pharmaceutical composition of claim 1 wherein the enhancer is olanzapine present at a concentration of about 0.1% to 25% w/v.

4. The pharmaceutical composition of claim 1 wherein the gelling agent is hydroxypropylcellulose.

5. The pharmaceutical composition of claim 1 wherein the form is a patch for transdermal delivery.

6. The pharmaceutical composition of claim 1 wherein the dosage form is an ointment, cream, emulsion, or liposome.

7. The pharmaceutical composition of claim 1 further comprising about PEG, ethanol, water, and hydroxypropylcellulose.

8. The pharmaceutical composition of claim 7, further comprising about 25% PEG, about 35% ethanol, about 0.5% hydroxypropylcellulose, and q.s. water.

9. A pharmaceutical composition comprising fluoxetine in a dosage form for transdermal delivery, wherein the composition is in liquid form, comprising:

- fluoxetine in the amount of about 0.1% to 40% w/v;

- optionally, an enhancer selected from the group consisting of olanzapine, clozapine, amoxapine, piperazine, 1-methylpiperazine, and combinations thereof.

10. The pharmaceutical composition of claim 9 wherein the enhancer is present at a concentration of about 0.1% to 25% w/v.

11. The pharmaceutical composition of claim 9 wherein the dosage form is a patch for transdermal delivery.

12. The pharmaceutical composition of claim 9 further comprising about PEG, ethanol, and water.

13. The pharmaceutical composition of claim 12 further comprising about 25% PEG, about 35% ethanol, and q.s. water.

14. A pharmaceutical composition comprising olanzapine in a dosage form for transdermal delivery, wherein the composition is in gel form, comprising:

- olanzapine in the amount of about 0.1% to 25% w/v; and
- a gelling agent in the range of about 0.1% to 5% w/v.

15. The pharmaceutical composition of claim 14 wherein the gelling agent is hydroxypropylcellulose.

16. The pharmaceutical composition of claim 14 further comprising about PEG, Ethanol, and water.

17. The pharmaceutical composition of claim 14 further comprising about 25% PEG, about 35% ethanol, and q.s. water.

18. The pharmaceutical composition of claim 14 wherein the dosage form is a patch for transdermal delivery.

19. The pharmaceutical composition of claim 14 being in the dosage form of an ointment, cream, emulsion, or liposome.

20. A pharmaceutical composition comprising olanzapine in a dosage form for transdermal delivery, wherein the composition is in liquid form, comprising:

- olanzapine in the amount of about 0.1% to 25% w/v.

21. The pharmaceutical composition of claim 20 further comprising PEG, ethanol, and water.

22. The pharmaceutical composition of claim 20 wherein the dosage form is a patch for transdermal delivery.

23. The pharmaceutical composition of claim 20 further comprising about 25% PEG, about 35% ethanol, and q.s. water.

Figure 1

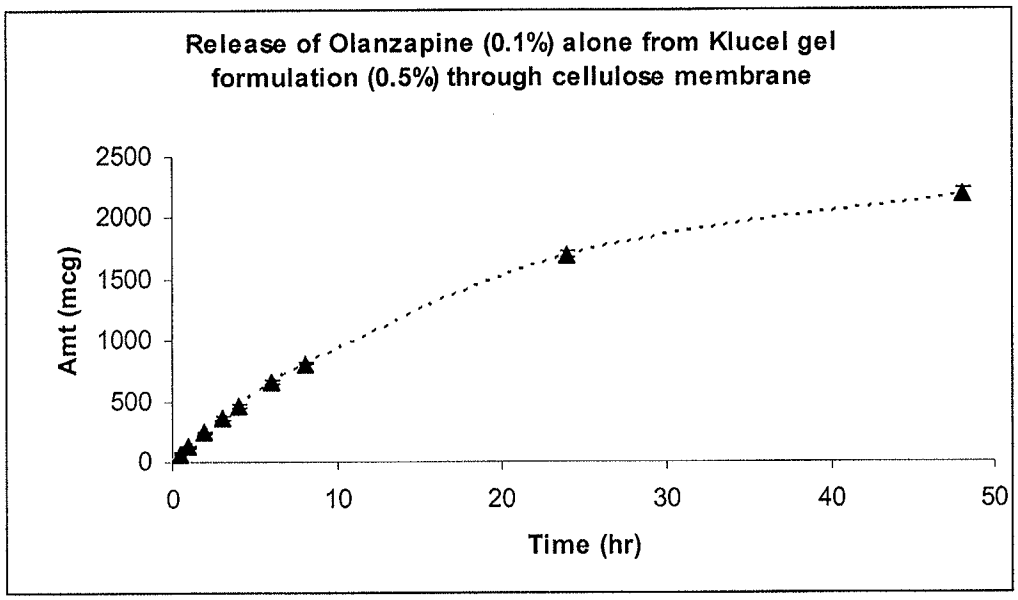

Release of Olanzapine (0.1%) alone from Klucel gel formulation (0.5%) through cellulose membrane
Amt (mcg)
2500
2000
1500
1000
500
0
0
10
20
30
40
50
Time (hr)

Figure 2

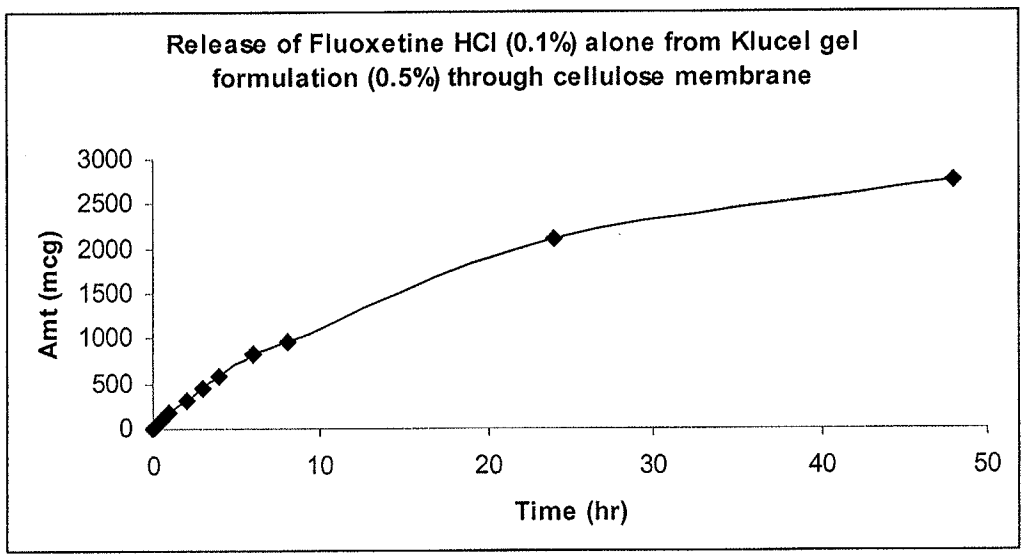

Release of Fluoxetine HCl (0.1%) alone from Klucel gel formulation (0.5%) through cellulose membrane
Amt (mcg)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
Time (hr)

Figure 3

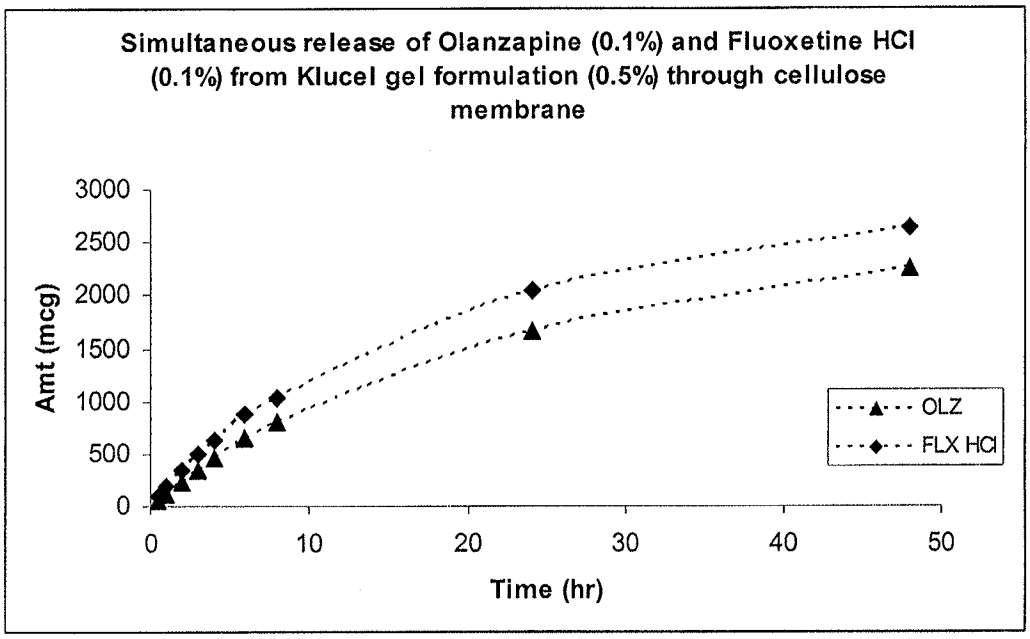

Simultaneous release of Olanzapine (0.1%) and Fluoxetine HCl (0.1%) from Klucel gel formulation (0.5%) through cellulose membrane
Amt (mcg)
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
Time (hr)
OLZ
FLX HCl

Figure 4

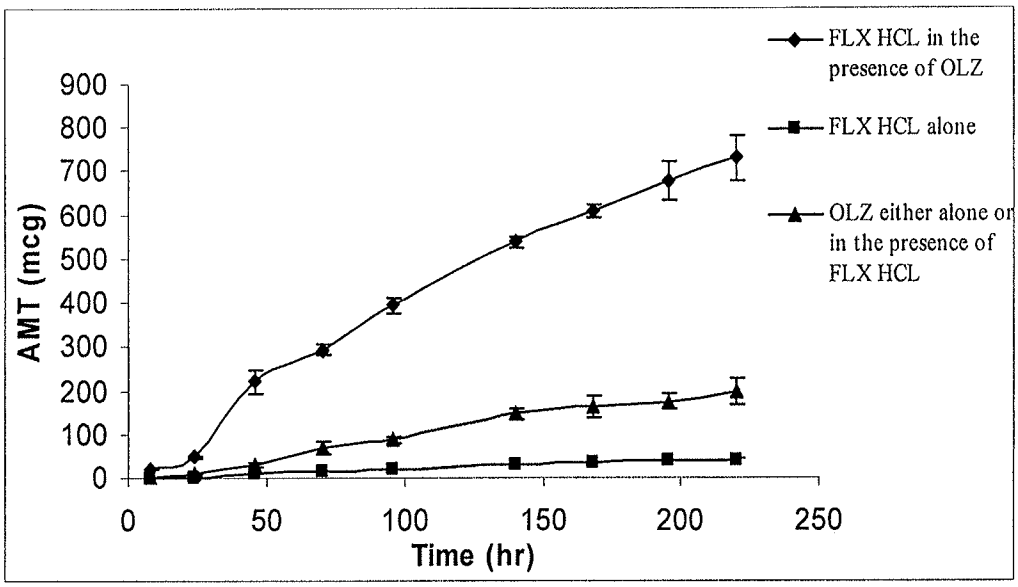

FLX HCL in the presence of OLZ
FLX HCL alone
OLZ either alone or in the presence of FLX HCL
AMT (mcg)
900
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (hr)

Figure 5

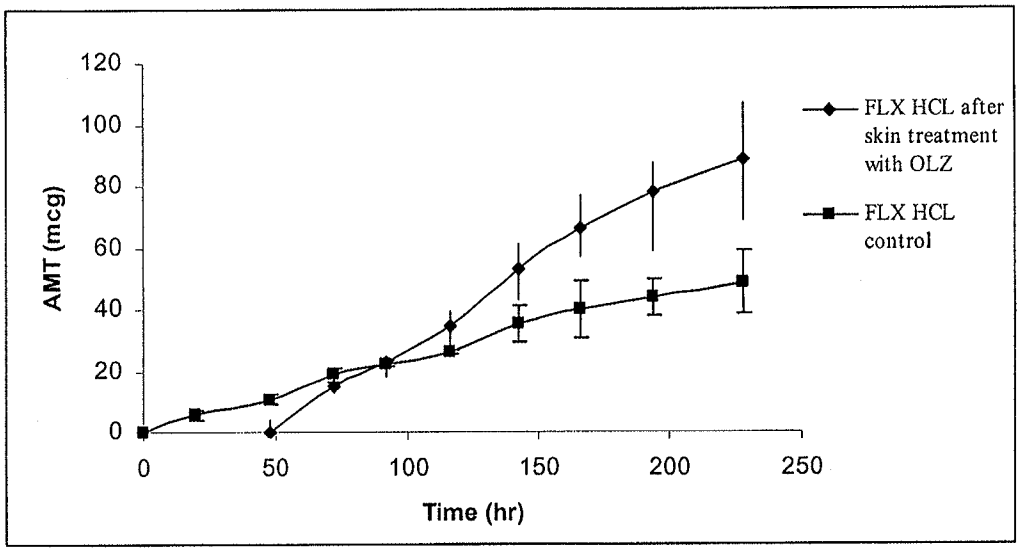
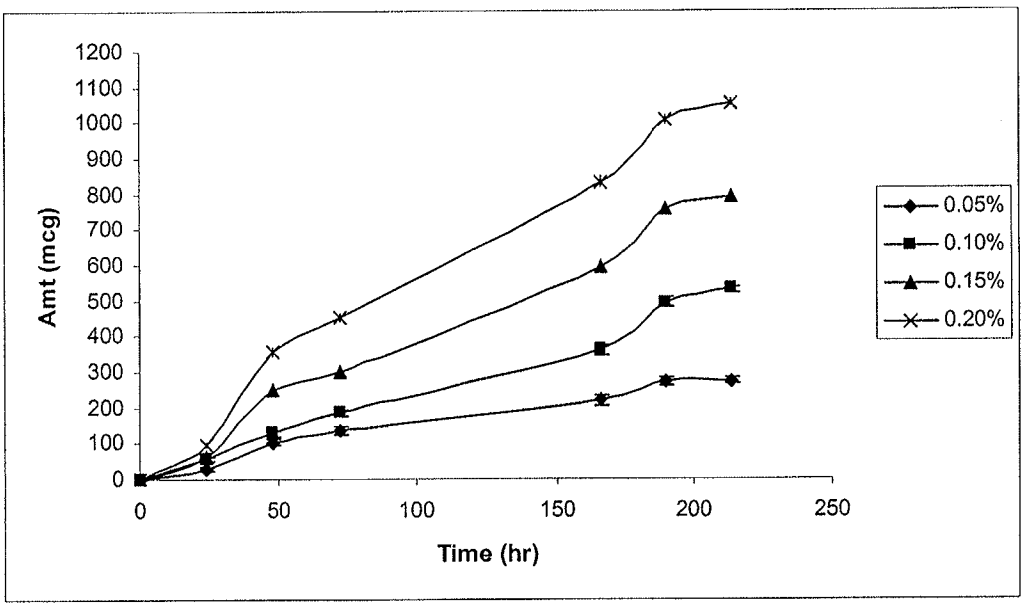

120
100
80
60
40
20
0
AMT (mcg)
0
50
100
150
200
250
Time (hr)
FLX HCL after skin treatment with OLZ
FLX HCL control

Figure 6


1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Amt (mcg)
0
50
100
150
200
250
Time (hr)
0.05%
0.10%
0.15%
0.20%

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/34150

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 213/00 (2014.01)
USPC - 564/347
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(8) - C07C 213/00 (2014.01)
USPC - 564/347

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Patents and NPL (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase (AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO), PubWest, Google Web
search term: Transdermal skin topical patch dressing Fluoxetine Prozac Sarafem Ladose Fontex Olanzapine Zyprexa Zypadhera Lanzek gel gelling liquid hydroxypropylcellulose dosage dosing dose ointment cream emulsion liposome

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0186277 A1 (Gale et al.) 25 August 2005 (25.08.2005), para [0053], [0054], [0085], [0096], [0117]-[0119], [0121], [0149]-[0150]; Table 4	1-13
X	US 2011/0178114 A1 (Aung-din) 21 July 2011 (21.07.2011), para [0031], [0042], [0051], [0171], [0181], [0188]-[0189], [0203]	14-23
Y	US 2005/0196418 A1 (Yu et al.) 8 September 2005 (08.09.2005), para [0028], [0030], [0091]-[0093], [0095], [0111]-[0114]	1-23
Y	US 2012/0196877 A1 (Singh) 2 August 2012 (02.08.2012), para [0012], [0039], [0055], [0056], [0076], [0079], [0099], [0108], [0121], [0166]-[0176]	1-23
Y	US 2003/0212060 A1 (Tollefson et al.) 13 November 2003 (13.11.2003), para [0086]-[0092], [0094], [0096], [0105]	1-3, 9-11
Y, P	US 2013/0171237 A1 (Plakogiannis et al.) 4 July 2013 (04.07.2013), para [0007]-[0008], [0011]-[0012], [0017], [0019], [0024], [0026]	1-23

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

* 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	Date of mailing of the international search report
12 August 2014 (12.08.2014)	29 AUG 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)