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(54) Title: COMPOSITION AND METHOD FOR AIDING SLEEP

(57) Abstract: Described is a controlled-release formulation for treating disturbed sleep or insomnia. The formulation is formulated to release a compound or combination of compounds in sequence at multiple stages.

## COMPOSITION AND METHOD FOR AIDING SLEEP

### CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to US Provisional Patent Application No. 61/936,566,  
5 filed on February 6, 2014, the entire content of which is hereby incorporated by reference  
herein.

### BACKGROUND

In patients suffering sleep disruptions, one can observe a clear distinction between the  
ability to fall asleep and the ability to remain asleep long enough to feel rested.  
10 Pharmacological therapeutics for insomnia typically focus on enabling a patient to fall asleep.  
Most patients taking sleeping pills wake up in the middle of night without completing the 8-  
hour sleep cycle. There is a need for drugs that allow a patient to fall asleep and stay asleep  
for a sufficient period of time.

### SUMMARY

15 Described below is a controlled-release formulation. The formulation includes one  
or more compounds for aiding sleep, wherein the formulation is formulated for releasing each  
compound at a specific time and a specific dose in a subject after the formulation is  
administered to the subject.

In one embodiment, the formulation is formulated for two to twelve stages of release,  
20 wherein each stage initiates release of a compound or a combination of compounds in a  
subject at a specific time point after administration of the formulation to the subject. For  
example, the time interval between the initiation of each stage of release can be 0.5 to 23  
hours. The first stage can be for immediate release of a compound or combination of  
compounds.

25 The compound or compounds can be selected from the group consisting of  
barbiturates (e.g., amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal),  
and phenobarbital (Luminal); benzodiazepines (e.g., clonazepam (Klonopin N.America;  
Rivotril Europe, Asia ), diazepam (Valium), estazolam (Prosom), flunitrazepam (Rohypnol),  
lorazepam (Ativan), midazolam (Versed), nitrazepam (Mogadon), oxazepam (Serax),  
30 triazolam (Halcion), temazepam (Restoril, Normison, Planum, Tenox, and Temaze),  
chlordiazepoxide (Librium), and alprazolam (Xanax)); non-benzodiazepine "Z-drugs"

sedatives (e.g., eszopiclone (Lunesta), zaleplon (Sonata), zolpidem (Ambien), and zopiclone (Imovane, Zimovane)); antihistamines (e.g., diphenhydramine, dimenhydrinate, doxylamine, mirtazapine, and promethazine); plant components or extracts (from, e.g., Duboisia hopwoodii, chamomile, Prostanthera striatiflora, catnip, kava (Piper methysticum), valerian, cannabis, and passiflora (e.g., Passiflora incarnata)); Validol; chloral hydrate; trazodone; opiates and opioids; Suvorexant (MK-4305, Merck & Co.); glutethimide; and  $\gamma$ -hydroxybutyric acid.

In one embodiment, the formulation is a tablet or capsule for oral administration. The tablet or capsule can contain a plurality of particles, each particle including a drug core and a polymeric composition encapsulating the core, wherein the drug core contains the one or more compounds for aiding sleep.

Also described is a method of treating disturbed sleep or insomnia in a subject. The method includes administering the above-described formulation to a subject in need thereof.

The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages of the embodiments will be apparent from the description and from the claims.

## DETAILED DESCRIPTION

It was unexpectedly discovered that administering certain drugs or combinations of drugs sequentially can both induce and maintain sleep in patients having disturbed sleep or insomnia. This approach extends sleep time while utilizing lower than recommended doses of the drugs, which reduces the risk of addiction and other side effects (e.g., next-morning impairment).

### Disturbed Sleep

As used herein, the term “disturbed sleep”, “sleep disturbances,” or “sleep disruption” refers to a condition characterized by waking up feeling unrestored, waking up in the middle of the night, difficulty returning to sleep after waking, difficulty falling asleep, and/or waking too early. Stress, a health condition, pain, a medication, jet lag, and noise are some factors that can lead to disturbed sleep. Disturbed sleep can be acute (i.e., short-termed) or chronic in duration.

An individual with insomnia experiences frequent and long-term disturbed sleep with daytime impairment or distress despite having adequate opportunity and circumstance for sleep.

Disturbed sleep can have various negative consequences such as fatigue, lack of energy, initiative reduction, daytime sleepiness, tension headache, gastrointestinal symptoms, irritability, anxiety, mood disturbance, reduced motivation, and impairment in cognitive functions (attention, concentration, and memory).

Whether a subject has disturbed sleep or insomnia can be determined by a skilled practitioner in the art.

10

#### Controlled-Release Formulation

Described herein is a controlled-release formulation containing one or more compounds or compositions for aiding sleep (e.g., sedative or hypnotic agents).

Such compounds or compositions for aiding sleep include, but are not limited to, barbiturates (e.g., amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal), and phenobarbital (Luminal)); benzodiazepines (e.g., clonazepam (Klonopin N.America; Rivotril Europe, Asia ), diazepam (Valium), estazolam (Prosom), flunitrazepam (Rohypnol), lorazepam (Ativan), midazolam (Versed), nitrazepam (Mogadon), oxazepam (Serax), triazolam (Halcion), temazepam (Restoril, Normison, Planum, Tenox, and Temaze), chlordiazepoxide (Librium), and alprazolam (Xanax)); non-benzodiazepine "Z-drugs" sedatives (e.g., eszopiclone (Lunesta), zaleplon (Sonata), zolpidem (Ambien), and zopiclone (Imovane, Zimovane)); antihistamines (e.g., diphenhydramine, dimenhydrinate, doxylamine, mirtazapine, and promethazine); plant components or extracts (e.g., components or extracts from *Duboisia hopwoodii*, chamomile, *Prostanthera striatiflora*, catnip, kava (*Piper methysticum*), valerian, cannabis, and passiflora (e.g., *Passiflora incarnata*)); Validol; chloral hydrate; trazodone; opiates and opioids; Suvorexant (MK-4305, Merck & Co.); glutethimide; and  $\gamma$ -hydroxybutyric acid. Other sedatives or hypnotic agents that target neurotransmitter receptors (e.g., histamine, GABA, and orexin receptors) can also be used in the formulation.

In one embodiment, the controlled-release formulation is formulated to release one compound/composition or one combination of compounds/compositions for aiding sleep. The formulation releases the compound/composition or combination of compounds/compositions at multiple stages (e.g., 2 to 12 stages). Each stage initiates release

of the compound/composition or combination of compounds/compositions at a specific time after administration of the formulation.

For example, the formulation can release a first dose of a compound immediately, release a second dose of the same compound 1 hour after release of the first dose, and then  
5 release a third dose of the compound 2 hours after release of the second dose.

In one embodiment, the controlled-release formulation releases two or more compounds/compositions or combinations of compounds/compositions for aiding sleep. The formulation releases the compounds or compositions at multiple stages (e.g., 2 to 12 stages). Each stage initiates release of a specific compound/composition or combination of  
10 compounds/compositions at a specific time after administration of the formulation to a subject.

For example, the formulation can release immediately a first compound, release a second compound 30 minutes after the release of the first compound, and then release a third compound and a fourth compound together 3.5 hours after the release of the second  
15 compound. In another example, the formulation can release a first compound at time 0, 2 hours, 4 hours, and 6 hours, and a second compound at time 1 hour, 3 hours, 5 hours, and 7 hours.

The time interval between the initiation of each stage of release can be 30 minutes to 23 hours (e.g., 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5  
20 hours, 5.5 hours, 6 hours, 6.5 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12.5 hours, 13 hours, 15 hours, 20 hours, 22 hours, and 23 hours). Each stage can release a dose of a compound in the range of 0.01 mg to 100 mg (e.g., 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, and 100 mg).

25 The first stage of release can be an immediate release, in which release of one or more active agents is initiated shortly (e.g., within 30 minutes) after administration of the formulation. The first stage of release can also be a delayed release.

The above-described controlled-release formulation can be a tablet (e.g., a pill) or a capsule (e.g., a hard-shelled capsule or a softgel) for oral administration. Other formulations  
30 such as implants and patches can also be used.

Methods for formulating and making controlled-release formulations are known in the art. See, e.g., Hong Wen and Kinam Park, 2010, *Oral Controlled Release Formulation*

*Design and Drug Delivery: Theory to Practice*, John Wiley & Sons, Inc. For example, controlled-release formulations can be designed based on particular physical mechanisms, e.g., dissolution, diffusion, osmosis, and ion exchange.

In a dissolution system, a drug is surrounded by or distributed in a polymeric composition (e.g., a polymeric membrane or a polymeric matrix). The drug is released when the polymeric composition dissolves. Properties of the polymeric composition, e.g., thickness and dissolution rate, determine drug release. In a diffusion system, the active ingredient has to diffuse through a polymeric composition (e.g., a polymeric membrane or a polymeric matrix) in order to be released. In an osmosis-based formulation, the drug is encapsulated by a polymeric coating that swells and erupts from osmotic pressure, thereby releasing the drug. Ion exchange formulation relies on attaching drug molecules to ionic groups. The drug molecules are then displaced by other ions and released. The controlled-release formulation described herein can utilize one release mechanism or a combination of release mechanisms.

In one embodiment, the above-described controlled-release formulation can be a tablet with multiple cores or layers. For example, the drug or combination of drugs for each stage of release can be surrounded by polymeric layer. The drug or combination of drugs is released as the layer dissolves.

In one embodiment, a multiparticulate system is employed. In this system, the active compounds are each delivered in multiple particles (e.g., small beads or microspheres ranging from 0.05 to 3.00 mm in size), each particle exhibiting the desired characteristics (e.g., release time and rate). For example, the above-described controlled-release formulation can include a plurality of particles. Each particle contains a core including a compound or combination of compounds for aiding sleep and a controlled-release polymeric composition (containing one or more polymers) encapsulating the core. Properties of the controlled-release polymeric composition in each particle determine the drug release profile of each particle. The formulation can include uncoated particles for immediate release of a drug. Any of the above-described or other release mechanisms (e.g., dissolution, diffusion, and osmosis) can be employed in a multiparticulate system. The plurality of particles can be encapsulated in a capsule or compressed into a tablet for oral administration. For example, a three-stage release formulation can contain three types of particles, each type for each stage of release. Each dose of a drug for each stage of release is delivered by multiple particles.

Natural and synthetic polymers for controlled-release formulations are known in the art. Such polymers include, but are not limited to, proteins, polysaccharides, nucleotides, alginate, chitosan, heparin, xanthan gum, starch, pectin, gelatin,  $\kappa/\tau$ -carrageenan, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, ethycellulose, methylcellulose, polyvinyl alcohol, polyacrylic acid, polyethylene oxide, poloxamers, pluronics, polymethacrylate, cellulose, collagen, nylon, polyalkylcyanoacrylate, polyethylene, polyethylene-co-vinylacetate, polyhydroxyethyl methacrylate, polyhydroxypropylethyl methacrylate, polymethyl methacrylate, polyurethane, and silicon. Commercially available polymers for pharmaceutical applications include EUDRAGIT® polymethacrylates.

In one embodiment, the controlled-release formulation employs an enteric coating or other coatings for delaying drug release until the drug reaches the small intestine or the colon. Delaying drug release in this manner would also control drug release time. Such coatings are known in the art.

When a compound or composition is released, it becomes available to the body. Each stage of release can have a specific release rate. For example, a stage can have a pulsatile-release profile, in which a drug is released rapidly and completely following a period of no release. A stage can also have a first-order release rate, in which a drug is released at a decreasing release rate. A zero-order release rate, i.e., a constant release rate, can also be employed. An entire dose (or a significant portion thereof) of a compound can be released within a short period or over an extended period. For example, the formulation can be designed to release at least 50% (e.g., more than 60%, 70%, 75%, 80%, 85%, 90%, or 95%) of a dose of a compound within 30 minutes of the initiation of release.

The controlled-release formulation can also include one or more pharmaceutical excipients, e.g., binders, plasticizers, lubricants, diluents, fillers, coloring agents, flavoring agents, glidants, and preservatives.

The controlled-release formulation can be administered to a patient daily or as needed to induce and maintains sleep.

The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein,

utilize the present disclosure to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

Example 1: A three-stage release formulation

5 A formulation, in tablet or capsule form, releases drugs at three stages. At the first stage, release of 50 mg of Benadryl starts immediately after uptake. At the second stage, release of 5 mg of Ambien starts 2-3 hours after the initiation of the release of Benadryl. 2-3 hours after the start of the second stage, release of 0.5 mg of Activan is initiated.

10 Example 2: A three-stage release formulation

A formulation, in tablet or capsule form, is formulated to initiate immediate release of 50 mg of Benadryl, 10 mg of melatonin, and 25 mg of Theanine upon uptake. 2 hours thereafter, release of 5 mg of Ambien is initiated. 3 hours after the start of the release of Ambien, release of 0.5 mg of Activan and 1 mg of Xanax are initiated.

15

Example 3: *In vitro* release profile of a three-stage release formulation

Hard gelatin capsules for releasing diphenhydramine HCl (i.e., 2-(diphenylmethoxy)-N,N-dimethylethanamine), zolpidem tartrate (i.e., N,N-dimethyl-2-(6-methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl)acetamide), and lorazepam (i.e., (RS)-7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one) were manufactured.

The capsules were designed to release the three drugs in a staged sequence controlled via pH-dependent coatings: uncoated diphenhydramine HCl for immediate release, coated zolpidem for release about 2 hours after administration, and coated lorazepam for release about 4 hours after administration.

25 Each capsule contained the following agents: (1) 50 mg of uncoated diphenhydramine HCl; (2) 5 mg of zolpidem tartrate in multiparticulate form coated with EUDRAGIT® L30 D-55, which dissolves at above pH 5.5 (with half-maximal drug release at pH 5.8 and maximal release at pH 6.3); and (3) 0.5 mg of lorazepam in multiparticulate form coated with EUDRAGIT® L/S 12,5 (1:1), which dissolves at above pH 6.5 (with half-maximal drug  
30 release at pH 7.2). The coatings were selected to achieve release of zolpidem tartrate with gastric emptying and release of lorazepam when the drug reaches the intestines.

Six capsules were individually tested in beakers for pH-dependent release of each active agent. As shown in Table 1, at pH 2, more than 89% of diphenhydramine HCl was released within 30 minutes, whereas neither zolpidem tartrate nor lorazepam was released. At pH 6.4, more than 71% of zolpidem tartrate, but not lorazepam, was released within 30 minutes. At pH 7.2, more than 70% of lorazepam was released within 30 minutes.

Table 1. pH-dependent release of diphenhydramine, zolpidem, and lorazepam from capsules.

Cap#	At 30 min in pH 2 (At time zero pH 2)			At 150 min in pH 6.4 (At 120 min changed to pH 6.4)			At 270 min in pH 7.2 (At 240 min changed to pH 7.2)		
	% Release			% Release			% Release		
	Diph	Zolp	Lora	Diph	Zolp	Lora	Diph	Zolp	Lora
1	93.4	0	0	98.0	76.4	0	99.9	91.0	81.3
2	89.8	0	0	100	68.2	0	100	98.7	77.2
3	98.2	0	0	99.9	79.4	0	99.8	99.1	80.1
4	98.7	0	0	100	76.2	0	99.1	100	83.2
5	96.8	0	0	100	71.3	0	100	97.6	70.2
6	97.3	0	0	99.9	80.1	0	99.2	99.1	72.1

Diph: diphenhydramine  
 Zolp: zolpidem  
 Lora: lorazepam

Example 4: Sleep study in dogs

The capsules described in Example 3 above were tested in dogs at CARE Research in Fort Collins, Colorado. Sleep pattern of dogs is polyphasic. Each bout of sleep ranges from a few minutes to about 45 minutes. Dogs follow circadian rhythm. They fall asleep from time to time during day-time but gain most of their needed sleep during night-time.

On Day 1, four normal, untreated Beagle dogs were housed individually and monitored by video-cameras mounted above continuously for 24 hours.

On Day 3, each dog was orally fed with one capsule in the morning, housed individually in the same room as in Day 1, and monitored by video-cameras mounted above continuously for 24 hours.

Recorded videos from 12 noon to 8 pm on Day 1 and Day 3 were analyzed. Time of each sleep bout by each dog was measured and total sleep time of each dog in the course of 8 hours was tallied. Table 2 below summarizes the test results.

As shown in Table 2, the capsules led to a significant increase in total sleep time in all four treated Beagle dogs.

Table 2. Effects of capsules on total sleep time in Beagle dogs.

5

Dog #	Total Sleep Time		Difference between Day 1 and Day 3	
	Day 1 Placebo	Day 3 Treated	Increase (min)	% Increase
1501	152 min	288 min	136 min	89.5%
1502	128 min	280 min	152 min	118.8%
1503	145 min	256 min	111 min	76.6%
1504	160 min	297 min	137 min	85.6%

#### Example 5: Sleep study in human subjects

For human studies, hard gelatin capsules identical to those described in Example 3 were manufactured, except that lorazepam was coated with EUDRAGIT® L 12,5 instead of EUDRAGIT® L/S 12,5 (1:1) to account for the slight differences between the gastrointestinal pHs of dogs and humans. EUDRAGIT® L 12,5 dissolves at above pH 6.0.

It is anticipated that, after administration of the capsules to human subjects, diphenhydramine would be released immediately and be effective for up to 4 hours. Zolpidem would be released about 2 hours after administration and reach its  $t_{max}$  (i.e., time to maximum concentration in plasma) about 2 hours later. Lorazepam would be released about 4 hours after administration of the capsules and reach its  $t_{max}$  about 6 hours post administration.

20

#### OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

25

From the above description, one skilled in the art can easily ascertain the essential characteristics of the described embodiments, and without departing from the spirit and scope

thereof, can make various changes and modifications of the embodiments to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

## WHAT IS CLAIMED IS:

1. A controlled-release formulation, comprising one or more compounds for aiding sleep, wherein the formulation is formulated for releasing each compound at a specific time and a specific dose in a subject after the formulation is administered to the subject.

2. The formulation of claim 1, wherein the formulation is formulated for releasing different compounds or different combinations of compounds at different time points in a subject after the formulation is administered to the subject.

3. The formulation of claim 1 or 2, wherein the formulation is formulated for releasing the one or more compounds at two or more stages, wherein, at each stage, release of a compound or a combination of compounds is initiated at a specific time in a subject after the formulation is administered to the subject.

4. The formulation of any of claims 1-3, wherein the formulation is formulated for two to twelve stages of release.

5. The formulation of any of claims 1-4, wherein the time interval between the initiation of each stage of release is 0.5 to 23 hours.

6. The formulation of any of claims 3-5, wherein the first stage is for immediate release of one or more compounds.

7. The formulation of any of claims 1-6, wherein the one or more compounds are selected from the group consisting of a barbiturate, diazepam, estazolam, flunitrazepam, lorazepam, midazolam, nitrazepam, oxazepam, triazolam, temazepam, chlordiazepoxide, alprazolam, eszopiclone, zaleplon, zolpidem, zopiclone, diphenhydramine, dimenhydrinate, doxylamine, mirtazapine, promethazine, a plant component or extract, Validol, chloral hydrate, trazodone, an opiate, an opioid, Suvorexant, glutethimide, and  $\gamma$ -hydroxybutyric acid.

8. The formulation of any of claims 1-7, wherein the formulation contains 0.01 mg to 100 mg of each of the one or more compounds.

9. The formulation of any of claims 1-8, wherein the formulation is a tablet or capsule for oral administration.

10. The formulation of claim 9, wherein the tablet is a multi-layered or multi-cored tablet.

11. The formulation of claim 9, wherein the tablet or capsule contains a plurality of particles, each particle including a drug core and a polymeric composition encapsulating the core, wherein the drug core contains one or more compounds for aiding sleep.

12. The formulation of any of claims 1-11, wherein the formulation is formulated for a first stage immediate release of an antihistamine, a second stage release of a benzodiazepine that starts 2-3 hours after initiation of the first stage, and a third stage release of a non-benzodiazepine sedative that starts 2-3 hours after initiation of the third stage.

13. The formulation of claim 12, wherein the antihistamine is diphenhydramine HCl, the benzodiazepine is zolpidem tartrate, and the non-benzodiazepine sedative is lorazepam.

14. The formulation of claim 13, wherein the formulation contains 50 mg of diphenhydramine HCl, 5 mg of zolpidem tartrate, and 0.5 mg of lorazepam.

15. The formulation of claim 14, wherein the formulation is a tablet or capsule for oral administration.

16. The formulation of claim 15, wherein the tablet or capsule contains a plurality of particles, each particle including a drug core and a polymeric composition encapsulating the core, wherein the drug core contains zolpidem tartrate or lorazepam.

17. The formulation of claim 16, wherein the polymeric composition includes a polymethacrylate.

18. The formulation of claim 16 or 17, wherein the drug core containing zolpidem  
5 tartrate is encapsulated by a first polymeric composition and the drug core containing lorazepam is encapsulated by a second polymeric composition, the first polymeric composition having a dissolution pH of above 5.5 and the second polymeric composition having a dissolution pH of above 6 or 6.5.

10 19. The formulation of any of claims 1-18, wherein the formulation contains diphenhydramine HCl, zolpidem tartrate, and lorazepam as the only three active compounds.

20. Use of the formulation of any of claims 1-19 for treating disturbed sleep or insomnia in a subject in need thereof.

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**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/22(2006.01)i, A61K 9/20(2006.01)i, A61K 47/30(2006.01)i**

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)

A61K 9/22; A61P 43/00; A61P 25/00; A61K 31/404; A61K 31/4045; A61K 31/515; A61K 31/519; A61P 25/20; A61K 9/24; A61K 9/20; A61K 47/30

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

Korean utility models and applications for utility models  
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) &amp; Keywords:aiding sleep, controlled-release formulation, insomnia, multiple stage

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008-0254121 A1 (CLEMENT, K. et al.) 16 October 2008 See abstract; claims 1-15; paragraphs [0002], [0025]-[0026], [0037]-[0038], [0041]-[0042]; figures 1-2.	1-3
X	US 2005-0031688 A1 (AYALA, W. J.) 10 February 2005 See abstract; claims 1-23, 32-36; paragraph [0110].	1-3
X	US 2013-0078304 A1 (HSIEH, HSIEN-JEN et al.) 28 March 2013 See abstract; claims 1-25.	1
A		2-3
A	US 2008-0248103 A1 (HEUER, M. et al.) 9 October 2008 See abstract; claims 1-6; paragraphs [0046]-[0048].	1-3
A	US 2013-0122092 A1 (STANKOV, B. M.) 16 May 2013 See abstract; claims 1-13.	1-3

 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

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"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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

24 April 2015 (24.04.2015)

Date of mailing of the international search report

**24 April 2015 (24.04.2015)**

Name and mailing address of the ISA/KR

International Application Division  
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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 10-11, 13-17  
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:  
Claims 10-11, 13-17 are unclear since they refer to multiple dependent claims which are not searchable due to not being drafted in accordance with the third sentence of Rule 6.4(a).
  
3.  Claims Nos.: 4-9, 12, 18-20  
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 an additional fees, this Authority did not invite payment of any 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 claims 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 claims 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.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2015/014393**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0254121 A1	16/10/2008	None	
US 2005-0031688 A1	10/02/2005	US 2009-041840 A1	12/02/2009
US 2013-0078304 A1	28/03/2013	None	
US 2008-0248103 A1	09/10/2008	US 7455864 B2 WO 2008-122104 A1	25/11/2008 16/10/2008
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