LIQUID PHARMACEUTICAL COMPOSITION

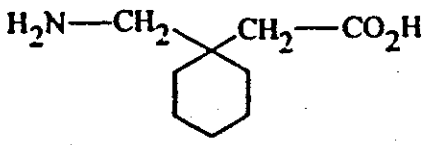
FIELD OF THE INVENTION

This invention relates to liquid pharmaceutical compositions comprising a gamma-aminobutyric acid (GABA) analog and processes for the preparation of the same as well as methods of using such compositions to treat subjects, including human subjects, suffering from certain cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas, neurodegenerative disorders, depression, mania and bipolar disorders, anxiety, panic, inflammation, renal colic, insomnia, gastrointestinal damage, incontinence, pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.

BACKGROUND OF THE INVENTION

GABA is an inhibitory amino acid found in the mammalian central nervous system (CNS). It has been reported that dysfunctions with GABA neurotransmission in the CNS may contribute or even cause psychiatric and neurological diseases such as epilepsy, schizophrenia, Parkinson's disease, Huntington's Chorea and dyskinesia (Saletu B., et al., *International Journal of Clinical Pharmacology, Therapy, and Toxicology*, 1986;24:362-373).

Gabapentin (1-(aminomethyl)-cyclohexaneocetic acid):

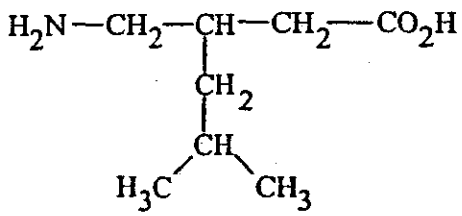


was designed as a GABA analog that would cross the blood-brain barrier. Gabapentin was found to have anticonvulsant and antispastic activity with extremely low toxicity in man. Gabapentin is presently marketed under the trademark Neurontin® as adjunctive therapy in the treatment of partial seizures in patients with epilepsy.

United States Patent Numbers *4,024,175* and *4,087,544* disclose the use of gabapentin for the treatment of certain forms of epilepsy, faintness attacks,

hypokinesia, and cranial traumas. Additionally, gabapentin brings about an improvement of cerebral functions and thus is useful in treating geriatric patients. United States Patent Number *5,084,479* discloses the use of gabapentin in neurodegenerative disorders. United States Patent Number *5,025,035* discloses the use of gabapentin in treating depression; United States Patent Number *5,510,381* discloses the use of gabapentin in treating mania and bipolar disorders. United States Patent Number *5,792,796* discloses the use of gabapentin in treating anxiety and panic. United States Patent Number *6,127,418* discloses the use of gabapentin in treating gastrointestinal damage; United States Patent Numbers *4,894,476* and *4,960,931* disclose a novel crystalline monohydrate form of gabapentin; and United States Patent Numbers *5,133,451*; *5,319,135*; *5,362,883*; *5,693,845*; *5,091,567*; and *5,068,413* disclose processes for preparing gabapentin as well as intermediates used in these processes. All of the aforementioned United States Patents are incorporated herein by reference.

Pregabalin ((S)-4-amino-3-(2-methylpropyl)butanoic acid)

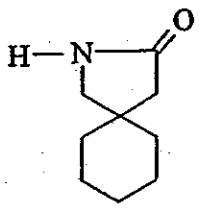


is another GABA analog disclosed in United States Patent Number *5,563,175* for the treatment of seizure disorders including epilepsy, which is herein incorporated by reference.

United States Patent Number *6,117,906* discloses the use of pregabalin in treating anxiety; United States Patent Number *6,001,876* discloses the use of pregabalin in treating pain; United States Patent Number *6,127,418* discloses the use of pregabalin in treating gastrointestinal damage; and United States Patent Numbers *5,599,973*; *5,608,090*; *5,684,189*; *5,710,304*; *5,616,793*; *5,629,447*; *5,637,767*; *5,840,956*; *6,046,353*; and *6,028,214* disclose processes for preparing pregabalin as well an intermediate used in these processes. All of the aforementioned United States Patents are incorporated herein by reference.

United States Patent Number *4,024,175* discloses the administration of gabapentin enterally or parenterally within wide dosage ranges in liquid and solid

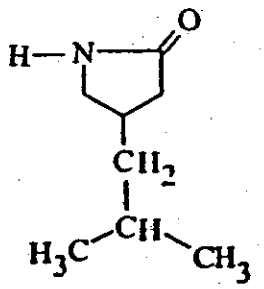
form. Subsequently, it was disclosed in United States Patent Number *6,054,482*, which is herein incorporated by reference, that gabapentin was converted to a lactam, i.e., 2-azaspiro[4.5]decan-3-one:



Furthermore, lactam formation unexpectedly occurred in the solid phase and under dry storage conditions. Since the gabapentin lactam displayed a certain toxicity, levels of this compound must be reduced to a minimum for reasons of safety. In further investigations, it was confirmed that liquid formulations of gabapentin undergo cyclization to form lactam much more readily than in the solid state. Additionally, it was discovered that gabapentin has a very bitter taste. Finally, there is a need to administer high doses of gabapentin in the treatment of certain diseases. In some cases, doses of up to 1500 mg per day are given to patients.

In view of the above issues, pharmaceutical compositions of gabapentin have been limited to solid dosage forms, such as capsules and tablets.

Pregabalin, similar to gabapentin, also is prone to cyclization to a lactam, i.e., 4-isobutyl-pyrrolidin-2-one:



Thus, there is a need for a liquid pharmaceutical composition of GABA analogs. In particular, liquid formulations of gabapentin and pregabalin would be desirable for the treatment of small children and elderly patients, since these patient groups require doses of gabapentin or pregabalin which are easy to swallow and which can be individually dosed.

The object of the present invention is a liquid pharmaceutical composition which is amenable to high concentrations of a GABA analog, is stable, has low levels of lactam, and has an agreeable taste.

We have surprisingly and unexpectedly found that a GABA analog can be formulated in a stable liquid pharmaceutical composition having low levels of the GABA analog lactam with a pH of about 5.5 to about 7.0 containing at least one polyhydric alcohol. Additionally, the present composition has an agreeable taste.

SUMMARY OF THE INVENTION

In an embodiment, there may be provided a liquid pharmaceutical composition of a GABA analog comprising at least one polyhydric alcohol containing 2 to 6 carbon atoms having a pH of about 5.5 to about 7.0.

In another embodiment, there may be provided a method for preparing a liquid pharmaceutical composition of a GABA analog comprising:
Step (1) adding a polyhydric alcohol containing 2 to 6 carbon atoms to water;
Step (2) adding a GABA analog to the solution from Step (1); and
Step (3) optionally adjusting the pH of the composition to about 5.5 to about 7.0 to afford the liquid pharmaceutical composition.

In yet another embodiment, there may be provided a two-component liquid pharmaceutical composition of a GABA analog comprising:

(a) a first component comprising a powder mixture of a GABA analog and a solid polyhydric alcohol;

(b) a second component comprising a liquid base wherein the powder component from (a) is added to the liquid base from (b) to afford a liquid pharmaceutical composition.

In still yet another embodiment, there may be provided a method for preparing a two-component liquid pharmaceutical composition of a GABA analog comprising:
Step (1) mixing a GABA analog with a solid polyhydric alcohol to afford a powder mixture;

Step (2) mixing a polyhydric alcohol with a sweetener and a flavor in water to afford a liquid base; and

Step (3) adding the powder mixture to the liquid base to afford the liquid pharmaceutical composition.

In a further embodiment, there may be provided a liquid pharmaceutical composition of a GABA analog having less than 0.5% by weight of its corresponding lactam.

In yet a further embodiment, there may be provided a method of using a liquid pharmaceutical composition of a GABA analog to treat subjects, including human subjects, suffering from cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas, neurodegenerative disorders, depression, mania and bipolar disorders, anxiety, panic, inflammation, renal colic, insomnia, gastrointestinal damage, incontinence, pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.

A first aspect of the present invention provides a liquid pharmaceutical composition comprising a GABA analog, water, and one or more polyhydric alcohols containing 2 to 6 carbon atoms, wherein the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition and the composition has a pH of about 5.5 to about 7.0.

A second aspect of the present invention provides a method for preparing a liquid pharmaceutical composition, the method comprising: (a) adding one or more polyhydric alcohols containing 2 to 6 carbon atoms to water to form a first solution; (b) adding a GABA analog to the first solution to form a second solution; and (c) optionally adjusting the pH of the second solution in a known manner to about 5.5 to about 7.0 to afford the composition, wherein the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition.

A third aspect of the present invention provides a pharmaceutical composition comprising: a first component comprising a powder mixture of a GABA analog and one or more polyhydric alcohols; and a second component comprising a liquid base, wherein the first and second components are combined to afford the composition in which the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition.

A fourth aspect of the present invention provides a method of preparing a liquid pharmaceutical composition, the method comprising: (a) mixing a GABA analog with a first polyhydric alcohol to afford a powder mixture; (b) mixing a second polyhydric alcohol with a sweetener and a flavor in water to afford a liquid base; and (c) combining the powder mixture and the liquid base to afford the composition, wherein the first and second polyhydric

and the liquid base to afford the composition, wherein the first and second polyhydric alcohols may be the same or different and together comprise about 25% to about 75% weight/volume of the composition.

A fifth aspect of the present invention provides a liquid pharmaceutical composition comprising gabapentin or pregabalin, water, and one or more polyhydric alcohols containing 2 to 6 carbon atoms, the composition having a pH of about 5.5 to about 7.0 and containing less than 0.5% by weight of gabapentin lactam or pregabalin lactam after storage at 2°C to 10°C for 18 months to 2 years, wherein the one or more polyhydric alcohols comprise at least 25% weight/volume of the composition.

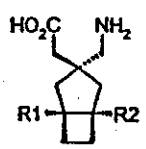
A sixth aspect of the present invention provides a use of a pharmaceutical composition according to the first aspect or the third aspect for the manufacture of a medicament for treating a subject suffering from cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas; neurodegenerative disorders; depression; mania and bipolar disorders; anxiety; panic; inflammation; renal colic; insomnia; gastrointestinal damage; incontinence; pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.

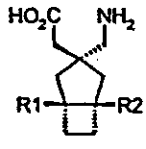
A seventh aspect of the present invention provides a use of a pharmaceutical composition according to the first aspect or the third aspect, wherein the pharmaceutical composition has less than 0.5% by weight of a corresponding lactam of the GABA analog for the manufacture of a medicament for treating a subject suffering from cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas; neurodegenerative disorders; depression; mania and bipolar disorders; anxiety; panic; inflammation; renal colic; insomnia; gastrointestinal damage; incontinence; pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.

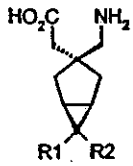
DETAILED DESCRIPTION OF THE INVENTION

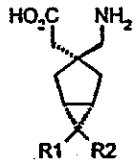
The term "polyhydric alcohol" refers to an alkyl or aliphatic alcohol containing from 2 to 6 carbon atoms and 2 to 6 hydroxyl groups, such as, for example, glycerol, xylitol, sorbitol, mannitol, and the like.

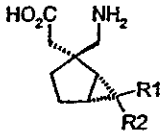
The term "GABA analog" refers to a compound derived from or based upon the structure of gamma-aminobutyric acid, such as, for example, gabapentin, pregabalin, and the like. Other GABA analogs that can be employed in the liquid pharmaceutical compositions of this invention are those referred to in Great Britian provisional patent application 0125807.8, which was filed on October 26, 2001, Great Britian provisional patent application 0109635.3, which was filed on April 19,2001, and the corresponding PCT patent application that claims priority from the two foregoing provisional applications and which was filed in April of 2002. The foregoing applications are incorporated herein by reference in their entirties. Examples of GABA analogs that are referred to in the foregoing references are set forth below.

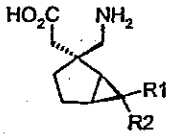

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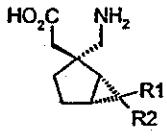

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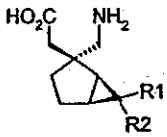

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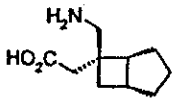

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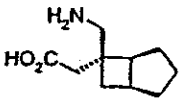

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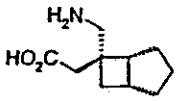

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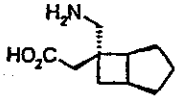

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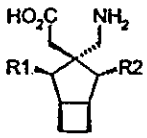

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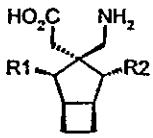

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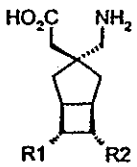

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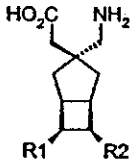

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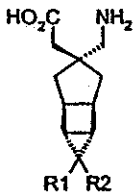

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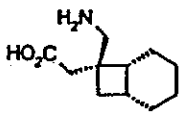

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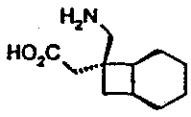

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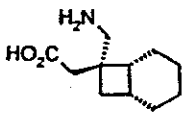

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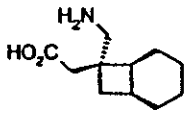

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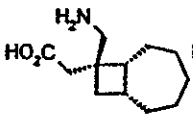

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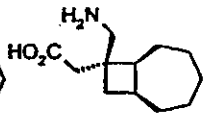

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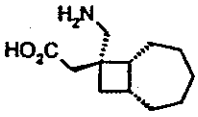

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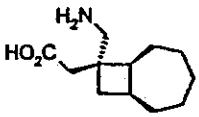

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wherein R^1 and R^2 are each independently selected from H, straight or branched alkyl of 1-6 carbon atoms, cycloalkyl of from 3-6 carbon atoms, phenyl and benzyl, subject to the proviso that, except in the case of a tricyclooctane compound of formula (XVII), R^1 and R^2 are not simultaneously hydrogen.

Suitable compounds (including salts, solvates and pro-drugs thereof) are: ((1R,5S)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1S,5R)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1R,5S)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;

((1S,5R)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid;

((1S,2S,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1R,2S,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1S,2R,5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1R,2R,5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid;

((1R,5R,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1S,5S,6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1R,5R,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

((1S,5S,6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid;

cis-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

trans-((1S,2R,4S,5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1S,5R,6S,7R)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1S,5R,6R,7S)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid;

((1R,2S,5S)-7-Aminomethyl-3,3-dimethyl-tricyclo[3.3.0.0]oct-7-yl)-acetic acid;

((1R,6R,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;

((1S,6S,7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;

((1R,6R,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;

((1S,6S,7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid;

((1R,7R,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;

((1S,7S,8S)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;

((1R,7R,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid;

((1S,7S,8R)-8-Aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid.

[(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid;

[(1S,5S,6R)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid;

(1RS,5RS,6RS)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid; and

[(1RS,6RS,7SR)-7-(Aminomethyl)bicyclo[4.2.0]oct-7-yl]acetic acid.

The liquid pharmaceutical compositions of the present invention comprise a GABA analog, such as, for example, gabapentin, pregabalin, and the like.

Gabapentin may readily be prepared as described in United States Patent Numbers *5,132,451*; *5,319,135*; *5,362,883*; *5,693,845*; *5,091,567*; and *5,068,413*.

Pregabalin may readily be prepared as described in United States Patent Numbers *5,563,175*; *5,599,973*; *5,608,090*; *5,684,189*; *5,710,304*; *5,616,793*; *5,629,447*; *5,637,767*; *5,840,956*; *6,046,353*; and *6,028,214*.

In preparing liquid pharmaceutical compositions of the compounds of the present invention, pharmaceutically acceptable carriers are solids and liquids.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or certain glycol solutions. For parenteral injections, liquid preparations can be formulated in solution in aqueous polyethylene glycol solutions.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, and stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as, natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

In the liquid pharmaceutical compositions of the present invention, it was found that if the formulation is buffered to a pH of about 5.5 to about 7.0 undesired lactam formation can be substantially avoided. However, this limits the use of certain adjuvants or carriers that can be used, such as, for example, taste-correcting acids or preservatives. Preservatives especially suited for oral compositions usually display their optimum antimicrobial activity in the acid range. Furthermore, the solubility of the usual preservatives, such as a paraben, sorbic acid, or benzoic acid decreases at low storage temperatures required for the liquid compositions of the present invention. Thus, precipitations and/or insufficient antimicrobial activity due to low concentration of the preservative at these low temperatures is to be expected. Salts of the usual preservatives have better solubility, but as a rule their antimicrobial activity is too weak.

In the development of the liquid pharmaceutical compositions of the present invention, it was shown that theoretically most alcohols possess a preserving and stabilizing action in aqueous solution. However, certain alcohols had undesirable properties and were not useful in the present pharmaceutical compositions. For example, ethyl alcohol is not desirable for pediatric formulations, propylene glycol and benzyl alcohol have an unpleasant taste, and chlorobutanol is not sufficiently stable at a pH of about 5.5 to about 7.0.

Surprisingly and unexpectedly, it was found that polyhydric alcohols containing 2 to 6 carbon atoms, preferably 3 to 6 carbon atoms, such as, for example, glycerol, xylitol, sorbitol, mannitol, and the like can be used as adjuvants for oral liquid gabapentin and pregabalin compositions. Preferably, glycerol and/or xylitol are used in the liquid compositions of the first aspect of the present invention. These adjuvants can be used in high concentration in the desired pH range of about 5.5 to about 7.0. Preferably, between a pH of about 6.0 to about 7.0. They not only act as preservatives and have a stabilizing effect on the

active components, but they also substantially mask the bitter taste of the active components as a result of their sweet taste and additionally are noncariogenic. Thus, the use of one or more polyhydric alcohols allows the preparation of acceptably tasting syrups of a GABA analog especially gabapentin or pregabalin which, when cooled to refrigeration temperatures of about 2° to about 10°C, have a storage stability of at least 2 years. The polyhydric alcohols may be used in a concentration range of about 25% to about 75% (weight/volume, w/v), preferably about 30% to 75% (w/v) and most preferably about 40% to about 75% (w/v). In general, it is not necessary to add additional preservatives to the liquid compositions of the present invention. However, the addition of another preservative may be advantageous (for example, in the case of sterile-filled syrups when the container is used for multiple doses to prevent contamination of the container). In the case of a sterile-filled syrup, care must be taken in choosing an additional preservative that can be used in the desired pH range (about 5.5 to about 7.0) that does not interact with the active components and does not accelerate lactam formation. We have found that benzethonium chloride can be used as an additional preservative.

Additionally, flavor improvers can be added to the liquid compositions of the present invention to enhance the taste masking action of the polyhydric alcohols. However, only adjuvants which do not contain a reactive aldehyde or keto functionality can be used, since these functionalities react with the active components. Furthermore, the flavor improvers must not alter the desired pH range of about 5.5 to about 7.0. For example, fruity compositions have proved to be especially effective, such as, for example, aniseed, strawberry and peppermint or aniseed, huckleberry, and peppermint, and the like.

A storage temperature of about 2°C to about 10°C, preferably about 2°C to about 8°C and more preferably about 4°C to about 7°C is required to ensure the stability of the active components and the taste of the liquid composition.

Furthermore, a liquid pharmaceutical composition of a GABA analog contains less than 0.5% (weight/weight, w/w) of the GABA analog lactam, preferably 0.4% (w/w) of lactam after storage at about 2°C to about 10°C, preferably about 2°C to about 8°C for 18 months to 2 years, preferably 18 months.

The syrup-like pharmaceutical compositions of the present invention can be filled into single or multiple dose containers. For example, single dose containers can be a double sachet of coated aluminum foil which contains two half doses. An example of multiple-dose containers are glass or plastic bottles, preferably with childproof closures. The multiple dose container is variable in dosage volume and can be provided with an appropriate dosage aid, such as, a measurement beaker, measurement pipette, and the like.

Another aspect of the present invention is a two-component liquid pharmaceutical composition of a GABA analog such as, for example, gabapentin, pregabalin and the like. The composition comprises a first component comprising a powder mixture of a GABA analog and a solid polyhydric alcohol, such as, for example, sorbitol, xylitol, mannitol, and the like, preferably sorbitol, and a second component comprising a liquid syrup base containing a polyhydric alcohol, such as, for example, glycerol and the like, and one or more flavoring agents, such as, for example, artificial menthol flavor, artificial aniseed flavor, artificial blueberry flavor, and sugar and water. The liquid pharmaceutical composition is prepared by dissolving the powder blend into the syrup vehicle at the time the product is dispensed to the patient. The liquid composition once prepared should be stored at about 2°C to about 10°C, preferably about 2°C to about 8°C, and more preferably about 4°C to about 7°C. However, the liquid composition may be stored at room temperature for about 2 months without exceeding undesired levels of lactam as previously described.

Dosages of gabapentin and pregabalin are well-known in the art, and the skilled practitioner will readily be able to determine the dosage amount required for a subject based upon weight and medical history.

In general, dosages of gabapentin and pregabalin are disclosed in the aforementioned United States Patents. In particular, dosages of gabapentin are disclosed in United States Patent Numbers *4,024,175*; *4,087,544*; and *6,054,482* and pregabalin in United States Patent Number *5,563,175*.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing and using the liquid pharmaceutical compositions of the present invention.

General Process for Preparing a Liquid Composition of Gabapentin

Water and glycerol are heated to 40°C to 50°C, and xylitol is added with stirring. An endothermic reaction results from the dissolution of the xylitol, and the solution is cooled. After the xylitol is dissolved, the solution is cooled to 30°C to 40°C, and gabapentin is added with stirring. After the gabapentin is completely dissolved, the flavor is added with stirring at 25°C to 30°C. The homogeneous solution is adjusted to a pH of 5.5 to 7.0, with an acid, such as, 0.1N hydrochloric acid (HCl), or base such as 0.1N sodium hydroxide (NaOH), and filtered.

Using the above general procedure, liquid compositions of pregabalin may be prepared.

Table 1 contains representative liquid compositions of gabapentin.

Table 1. Liquid Composition of Gabapentin

	Example 1[a]	Example 2	Example 3	Example 4
Gabapentin	2.000	5.000	5.000	5.000
Xylitol	20.000	30.000	30.000	29.940
Strawberry/anise flavor	1.000	–	–	1.000
Huckleberry/anise flavor	–	1.000	1.000	–
Glycerol 95%	50.000	40.000	30.000	43.790
Hydrochloric acid, 0.1N	–	7.720	–	–
Sodium hydroxide, 0.1N	–	–	0.770	–
Purified water	27.000	16.280	33.230	20.27
pH value	6.2	5.5	7.0	6.5

[a] Amounts are in grams per 100 mL.

General Process for Preparing a Two-Component Liquid Composition of Gabapentin

Step [A] Powder Blend

Gabapentin or gabapentin monohydrate (US Patent Number *4,894,476*) is blended with sorbitol.

Step [B] Syrup Base

A sorbitol solution, glycerol, granular sugar, menthol flavor, artificial aniseed flavor, and artificial blueberry flavor are dissolved in distilled water.

Step [C] Final Syrup

The syrup is prepared by dissolving the powder blend from Step [A] into the syrup base from Step [B]. The powder blend is stored in aluminum pouches and the syrup base is stored in a glass bottle at room temperature. After preparing the syrup extemporaneously, the syrup is stored under refrigeration.

Using the above general procedure, two-component liquid compositions of pregabalin may be prepared.

Table 2 contains a representative liquid composition of gabapentin.

Table 2. Two-Component Liquid Composition of Gabapentin

Powder Blend	
Gabapentin Monohydrate (Equivalent to 9.00 g gabapentin)	9.90 g
Sorbitol	22.50 g

Syrup Base	
Sorbitol Solution	225.00 g
Glycerin, USP	180.00 g
Sugar, Granular	45.00 g
Artificial Menthol Flavor[a]	56.25 mg
Artificial Aniseed Flavor[b]	22.50 mg
Artificial Blueberry Flavor	4.275 g
Water, Distilled	qs[c] to 450 mL

[a] Actually 2.5% solution of menthol in alcohol is weighed.

[b] Actually 2.5% solution of aniseed in water is weighed.

[c] Quantity sufficient

CLAIMS

1. A liquid pharmaceutical composition comprising a GABA analog, water, and one or more polyhydric alcohols containing 2 to 6 carbon atoms, wherein the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition and the composition has a pH of about 5.5 to about 7.0.

2. The composition according to claim 1, wherein the one or more polyhydric alcohols each contains 3 to 5 carbon atoms.

3. The composition according to claim 1, wherein the one or more polyhydric alcohols are selected from the group consisting of: glycerol, xylitol, sorbitol, mannitol, and a mixture of glycerol and xylitol, and wherein the one or more polyhydric alcohols comprise about 40% to about 75% weight/volume of the composition.

4. The composition according to claim 1, wherein the pH of the liquid pharmaceutical composition is about 6.0 to about 7.0.

5. The composition according to claim 1, further comprising at least one of a preservative and a flavor improver, wherein the flavor improver does not contain an aldehyde or keto functionality.

6. A method for preparing a liquid pharmaceutical composition, the method comprising: (a) adding one or more polyhydric alcohols containing 2 to 6 carbon atoms to water to form a first solution; (b) adding a GABA analog to the first solution to form a second solution; and (c) optionally adjusting the pH of the second solution in a known manner to about 5.5 to about 7.0 to afford the composition, wherein the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition.

7. The method according to claim 6, wherein the one or more polyhydric alcohols are glycerol and xylitol.

8. The method according to claim 6, wherein the one or more polyhydric alcohols comprise about 40% to about 75% weight/volume and the pH of the composition is about 6 to about 7.

9. A pharmaceutical composition comprising: a first component comprising a powder mixture of a GABA analog and one or more polyhydric alcohols; and a second component comprising a liquid base, wherein the first and second components are combined to afford the composition in which the one or more polyhydric alcohols comprise about 25% to about 75% weight/volume of the composition.

10. A method of preparing a liquid pharmaceutical composition, the method comprising: (a) mixing a GABA analog with a first polyhydric alcohol to afford a powder mixture; (b) mixing a second polyhydric alcohol with a sweetener and a flavor in water to afford a liquid base; and (c) combining the powder mixture and the liquid base to afford the composition, wherein the first and second polyhydric alcohols may be the same or different and together comprise about 25% to about 75% weight/volume of the composition.

11. The method according to claim 10, wherein the GABA analog is gabapentin or pregabalin.

12. The composition according to claim 1 or claim 9, wherein the GABA analog is gabapentin or pregabalin.

13. The composition according to claim 1 or claim 9, wherein the composition has less than 0.5% by weight of a corresponding lactam of the GABA analog.

14. A liquid pharmaceutical composition comprising gabapentin or pregabalin, water, and one or more polyhydric alcohols containing 2 to 6 carbon atoms, the composition having a pH of about 5.5 to about 7.0 and containing less than 0.5% by weight of gabapentin lactam or

15. Use of a pharmaceutical composition according to claim 1 or claim 9 for the manufacture of a medicament for treating a subject suffering from cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas; neurodegenerative disorders; depression; mania and bipolar disorders; anxiety; panic; inflammation; renal colic; insomnia; gastrointestinal damage; incontinence; pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.

16. Use of a pharmaceutical composition according to claim 1 or claim 9, wherein the pharmaceutical composition has less than 0.5% by weight of a corresponding lactam of the GABA analog for the manufacture of a medicament for treating a subject suffering from cerebral diseases, including epilepsy, faintness attacks, hypokinesia and cranial traumas; neurodegenerative disorders; depression; mania and bipolar disorders; anxiety; panic; inflammation; renal colic; insomnia; gastrointestinal damage; incontinence; pain, including neuropathic pain, muscular pain, skeletal pain, and migraine.