piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof.

[0022] Examples of the salt of citric acid include sodium citrate, disodium citrate, trisodium citrate, and others.

[0023] Examples of the salt of acetic acid include sodium acetate, potassium acetate, and others.

[0024] Malic acid may be in the form of racemate or enantiomer (L-body or D-body). Examples of the salt thereof include sodium malate, disodium malate, and others.

[0025] Examples of the amine include trometamol, monoethanolamine, diethanolamine, triethanolamine, meglumine, and others. Examples of the salt thereof include hydrochloride salt thereof, acetate salt thereof, and others. The amine of the present invention is preferably trometamol, and examples of the salt thereof include trometamol hydrochloride, and others.

[0026] Examples of the amino acid include ε-aminocaproic acid, glycine, alanine, valine, leucine, serine, threonine, methionine, ~~threonine,~~ glutamine, glutamic acid, asparagine, aspartic acid, arginine, lysine, histidine, and others. When they have optical isomers, they may be in the form of racemate or enantiomer (L-body or D-body). Examples of the salt thereof include hydrochloride salt thereof, acetate salt thereof, and others. The amino acid of the present invention is preferably ε-aminocaproic acid, glycine, L-

invention may be 0.001% (w/v), 0.002% (w/v), 0.005% (w/v), 0.01% (w/v), 0.02% (w/v), 0.05% (w/v), 0.1% (w/v), 0.2% (w/v), 1.5% (w/v), 2% (w/v), 3% (w/v), 4% (w/v), 5% (w/v), 6% (w/v), 8% (w/v), 10% (w/v) or 20% (w/v).

Also, in an embodiment of the pharmaceutical composition of the present invention, the lower limit of the amount of the buffering agent in the pharmaceutical composition of the present invention is preferably 0.1 part by mass, more preferably 1 part by mass, furthermore preferably 10 parts by mass, even more preferably 50 parts by mass, particularly preferably 100 parts by mass, and most preferably 500 parts by mass per part by mass of (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof. In another embodiment of the pharmaceutical composition of the present invention, the lower limit of the amount of the buffering agent in the pharmaceutical composition of the present invention is preferably 0.01 part by mass, more preferably 0.03 part by mass, furthermore preferably 0.05 part by mass, even more preferably 0.1 part by mass, particularly preferably 0.3 part by mass, and most preferably 0.5 part by mass per part by mass of (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof. Also, in an embodiment of the pharmaceutical

[0064]

[Table 1]

Formulation Examples %(w/v)	1	2	3	4	5	6	7	8	9	10
AFDX0250	0.1	1.0	0.01	0.2	0.5	0.5	0.1	0.2	0.001	1.5
Sodium acetate hydrate	0.15			0.5		0.25				
Sodium citrate hydrate			0.2		0.3		0.15	0.5		0.3
ε-Aminocaproic acid		0.3				0.1	0.1		0.25	
Sodium dihydrogen phosphate hydrate				0.25					0.2	
Trometamol	0.3		0.3			0.5				1.5
Boric acid		0.1			0.2		0.5			
Sodium chloride		q.s.	q.s.			q.s.				q.s.
Mannitol	q.s.				q.s.		q.s.			
Concentrated glycerin				q.s.				q.s.	q.s.	
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dilute hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	6.5	6	5	6	6.5	5	6.5	6	5	5.5
Osmotic pressure ratio	1	1	1	1	1	1	1	1	1	1

[0065]

[Table 2]

Formulation Examples %(w/v)	11	12	13	14	15	16	17	18	19	20
AFDX0250	0.05	0.1	0.001	1.5	0.3	0.2	0.1	0.5	0.2	0.5
Sodium acetate hydrate			0.2				0.15	0.2	0.25	
Sodium citrate hydrate		0.15		0.25	0.3	0.1				1.3
ε-Aminocaproic acid	0.2			0.1						
Sodium dihydrogen phosphate hydrate			0.5							
Trometamol		0.1		0.1		0.25		0.8		
Boric acid	0.25				0.2		0.5			
Sodium chloride		q.s.	q.s.			q.s.			q.s.	
Mannitol	q.s.				q.s.					q.s.
Concentrated glycerin				q.s.			q.s.	q.s.		
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dilute hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	6	6	5	6.5	5	6	6.5	5	5.5	6
Osmotic pressure ratio	1	1	1	1	1	1	1	1	1	1

[0066]

[Table 3]

Formulation Examples %(w/v)	21	22	23	24	25	26	27	28	29	30
AFDX0250	0.2	0.001	1.5	0.5	0.2	0.05	0.5	0.2	0.1	0.5
Sodium acetate hydrate		0.2				0.1				
Sodium citrate hydrate	0.1				0.3		0.15		0.25	0.3
ε-Aminocaproic acid			0.25			0.15			0.1	
Sodium dihydrogen phosphate hydrate	0.25			0.15				0.2		
Trometamol		0.2			0.3		0.1			0.5
Boric acid			0.5	0.1				0.2		
Sodium chloride				q.s.		q.s.	q.s.			
Mannitol	q.s.				q.s.			q.s.	q.s.	
Concentrated glycerin		q.s.	q.s.							q.s.
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dilute hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	5.5	6	5	5	6	5.5	6	6.5	6	5
Osmotic pressure ratio	1	1	1	1	1	1	1	1	1	1

[0067]

[Table 4]

Formulation Examples %(w/v)	31	32	33	34	35	36	37	38	39	40
AFDX0250	0.1	0.001	0.2	1.0	0.1	0.5	0.3	0.7	0.1	0.2
Sodium acetate hydrate	0.02				0.3			0.2		
Sodium citrate hydrate			0.2	0.25			0.25			
ε-Aminocaproic acid		0.05					0.2			
Sodium dihydrogen phosphate hydrate						0.25			0.15	0.3
Trometamol			0.4		0.01				0.3	0.2
Boric acid	0.5	0.2		0.05		0.2		0.5		
Sodium chloride	q.s.				q.s.		q.s.			
Mannitol		q.s.	q.s.						q.s.	q.s.
Concentrated glycerin				q.s.		q.s.		q.s.		
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dilute hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	6	5	5.5	6.5	5	5.5	6	6	6.5	6
Osmotic pressure ratio	1	1	1	1	1	1	1	1	1	1

[0068]

[Table 5]

Formulation Examples %(w/v)	41	42	43	44	45	46	47	48	49	50
AFDX0250	0.5	0.1	0.01	0.05	0.002	0.5	0.7	0.3	1.0	0.2
Sodium acetate hydrate		0.15			0.3			0.1	0.2	
Sodium citrate hydrate	0.1		0.2			0.1		0.05		0.15
ε-Aminocaproic acid									0.05	
Sodium dihydrogen phosphate hydrate				0.25		0.1				0.2
Trometamol	0.2			0.1	0.15		0.25		0.02	
Boric acid		0.05	0.2					0.5		
Sodium chloride				q.s.		q.s.			q.s.	q.s.
Mannitol	q.s.				q.s.			q.s.		
Concentrated glycerin		q.s.	q.s.				q.s.			
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Dilute hydrochloric acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	5.5	6	6	6.5	5	5	5.5	6.5	6	5
Osmotic pressure ratio	1	1	1	1	1	1	1	1	1	1

CLAIMS

1. A pharmaceutical composition with a pH of 6.5 or less comprising (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof.

2. The pharmaceutical composition according to claim 1, wherein the pH is 4 to 6.5.

3. A pharmaceutical composition comprising (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof and one or more buffering agents selected from the group consisting of citric acid, acetic acid, malic acid, an amine, an amino acid and a salt thereof.

4. The pharmaceutical composition according to claim 1 or 2, which comprises one or more buffering agents selected from the group consisting of citric acid, acetic acid, malic acid, an amine, an amino acid and a salt thereof.

5. The pharmaceutical composition according to claim 3 or 4 comprising citric acid or a salt thereof, wherein the pharmaceutical composition further comprises any of acetic

acid or a salt thereof, malic acid or a salt thereof, an amine or a salt thereof, or an amino acid or a salt thereof as a buffering agent.

6. The pharmaceutical composition according to any one of claims 3 to 5, wherein the amine is trometamol.

7. The pharmaceutical composition according to any one of claims 3 to 6, wherein the amino acid is ε-aminocaproic acid, glycine or L-glutamine.

8. The pharmaceutical composition according to any one of claims 3 to 5, wherein the buffering agent is citric acid or a salt thereof and trometamol or a salt thereof.

9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the content of (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof in the pharmaceutical composition is 0.0001 to 5% (w/v).

10. The pharmaceutical composition according to any one of claims 3 to 9, wherein the content of the buffering agent in the pharmaceutical composition is 0.001 to 10% (w/v).

11. The pharmaceutical composition according to any one of claims 3 to 10, wherein the content of the buffering agent in the pharmaceutical composition is 0.1 to 20000 parts by weight or 0.01 to 1000 parts by weight per part by weight of (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof.

12. The pharmaceutical composition according to any one of claims 1 to 11 for ocular topical administration

13. The pharmaceutical composition according to claim 12, wherein the ocular topical administration is instillation administration, conjunctival sac administration, intravitreal administration, sub-conjunctival administration or sub-Tenon's administration.

14. The pharmaceutical composition according to any one of claims 1 to 13 which is an eye drop, an eye gel or an injection.

15. The pharmaceutical composition according to any one of claims 1, 2 and 4 to 14 stored at 50°C or less.

16. A method of stabilizing (+)-11-[2-[2-

[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof in a pharmaceutical composition comprising the same, which comprises adjusting the pH of the pharmaceutical composition to 6.5 or less.

17. A method of stabilizing (+)-11-[2-[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one or a salt thereof in a pharmaceutical composition comprising the same, which comprises adding one or more buffering agents selected from the group consisting of citric acid, acetic acid, malic acid, an amine, an amino acid or a salt thereof into the pharmaceutical composition.