PHARMACEUTICAL COMPOSITION IN THE FORM OF A TABLET AND A METHOD FOR PRODUCING SAME

Field of the Invention

The invention relates to the field of medicine, the chemical-pharmaceutical industry and, in particular, to agents exhibiting nootropic and neuromodulating activity. It relates to new glutaryl histamine compositions and methods for producing same. In particular, glutaryl histamine formulations are mixed with various excipients for producing solid glutaryl histamine formulation.

In some embodiments a solid formulation is a tableted form, in other embodiments this is a capsule.

An additional aspect of this invention includes a method for producing preparative forms of glutaril histamine. Other aspects of this invention include use of these compositions for treatment of a viral disease in a mammal in need of this, which includes introducing a therapeutically efficient quantity of a composition according to this invention to this mammal.

Prior Art

Influenza presents a most serious problems among viral diseases.

Influenza is one of the most dangerous infection from the epidemical point of view. For example, annually about 7 million cases of an influenza virus infection are registered among 142 million of the population, which is about 20% in the structure of infectious and parasitic diseases, and this is a significant indicator (??). One of the evolutionary abilities of the influenza virus is its high ability to mutate quickly due to the antigen variability. Influenza viruses are widespread both in human beings and in several types of animals, including

mammals and birds. Thus, influenza viruses of some animals, e.g., birds and pigs, are the most pathogenic.

Vaccinal prevention is the most widespread form of acting upon an influenza virus. Vaccinotherapy gives good results in morbidity prevention and/or reduction in disease intensity. And even these measures cannot stop mass disease outbreaks, especially in the cold period of the year.

Mortality in cases of several influenza forms is more than 50%, even with high-technology methods of treatment. In such cases a disease, as other influenza forms of other etiology, is characterized by acute onset and severe clinical course, i.e., a high (40°C and higher) temperature and prolonged fever with intoxication symptoms - headache, insomnia, pain feelings in muscles and joints, meningeal symptoms. One of unfavorable clinical courses is an instant form, i.e., a quickly developing hemorrhagic toxic pulmonary edema and fatal outcome caused by respiratory failure and cardiovascular collapse [Int. J. Tuberc. Lung Dis. // 2007 - V.11. - N7. - P.710-721].

During influenza therapy Amantadine and Remantadine have been widely used – preparations that exhibit antiviral activity against influenza virus strains [Am. J. Med. - 1997. - V.102(3A) - N17. - P.55-60], [Watts J. «Asian nations step up action to curb spread of avian influenza» // Lancet. - 2004. - V.363 - N9406. - P.373]. The antiviral preparation Remantadine is widespread in the Russian Federation. It is used for treatment and prophylaxis of an infection caused by influenza viruses of A type. This preparation has shown a pronounced therapeutic effect in respect of the influenza virus of the H3N2 sub-type. The mechanism of action upon the virus is connected with blocking the viral protein function within the membrane. The virus activity is inhibited at the stages of receptor-mediated endocytosis, decapsidation in the phagolysosome as well as assembly and blastogenesis of virus particles [RAMN Vestnik (Bulletin

of the Russia Academy of Medical Sciences // 1993. No. 3. - p. 10-15]. However, Remantadine, as a representative of the adamantane group, has certain limitations in use. If a dose is high, side effects in the CNS appear, in particular, spasmodic effects. It also acts unfavorably on liver and kidneys due to which it is unlikely to be used for patients having diseases of these organs.

At present, inhibitors of neuraminidase of influenza viruses A and B are widely used, such as oseltamivir phosphate and zanamivir, which, by connecting to a hydrophobic region of an active region of neuraminidase of an influenza virus, blocks the latter's ability to detach remains of sialic acid from the surface of an infected cell, thus suppressing passage of newly formed virions out of it.

Oseltamivir is the trade name of Tamiflu®, zanamivir is the trade name of Relenza®; they are considered to be efficient antivirus preparations [Cheung C.L., Rayner J.M., Smith G.J. et al. Distribution 20 of amantadine-resistant H5N1 avian influenza variants in Asia // J. Infect. Dis. - 2006. - Vol.193. - P. 1626-1629]. At present, cases of appearing resistance to oseltamivir and zanamivir are reported [Menno D. de Jong, Tran Tan Thanh, Truong Huu Khanh et al. Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection // N. Engi. J. Med. - 2005. - N353. - P.2667-2572], [Smee D.F., Wong M.H., Bailey K.W., et al. Activities of oseltamivir and ribavirin used alone and in combination against infections in mice with recent isolates of influenza A (H1N1) and B viruses // Antivir Chem Chemother. - 2006. - V.17, N4. - P.185-192]. It is related to mutations in the gene coding the M_2 protein, which mutations make the virus resistant to this class of compounds [Li K.S., Guan Y., Wang J., et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia // Nature. - 2004. - V.430, N6996. - P.209-213], [Hui-Ling Y., Ilyshina N.A., Salomon R. et al. Neuraminidase inhibitor-

resistant recombinant A/Vietnam/1203/04 (H5N1) influenza viruses retain their replication efficiency and pathogenicity in vitro and vivo // J. Virol. - 2007. - Vol.81. - P.12418-12426; Le Q.M., Kiso M., Someya K. et al. Avian flu: isolation of drug-resistant H5N1 virus // 30 Nature. - 2005. - Vol.437. - P.1108]. According to some data, mutations appear in about 30% of cases. Also, neuraminidase inhibitors exhibit pronounced side effects in respect of the CNS. Thus, experts of the British Health Protection Agency gave their recommendations to the British Government to the effect that oseltamivir, or Tamiflu, should not be administered to children for A/H1N1 influenza prophylaxis due to a great number of unwanted side effects.

One of the most common preparations for treatment and prophylaxis of viral infections, including influenza, in the Russian Federation is Arbidol®. However, if it is administered orally against highly pathogenic strain of influenza virus A (H5N1) in vivo according to regimens of urgent prophylaxis and treatment (135 mg/kg of white mice body weight), the efficiency of its protection is only 25 and 10%, respectively. This protection level does not comply with the existing national requirements to efficiency of antivirus preparations (at least 30%) [see, "Manual for Experimental (Pre-Clinical) Studies of New Pharmacological Substances". - M., 2005. - p. 541].

Highly pathogenic virus diseases also include the severe acute respiratory syndrome (SARS) that is a new acute coronaviral disease caused by the agent of genotype IV and characterized by mortality up to 10% [Revised U.S. Surveillance case definition for severe acute respiratory syndrome (SARS) and update on SARS cases - United States and worldwide, December 2003 // MMWR Wkly Rep. - 2003. - Vol.52, N.49. - P.1202- 1206].

Summary of the Invention

this invention proposes , the method for producing a glutaryl histamine composition that does not comprises magnesium salts of silicic acids and/or talc. Other embodiments include glutaril histamine compositions comprising one or more diluents, disintegrators, binders and lubricants One practical embodiment proposes a composition that comprises glutaryl histamine and one or more diluents, disintegrators, binders and lubricants. Other preferable, but not exclusive, embodiments propose a composition comprising glutaril histamine, one or more diluents, said diluents being selected from starches, lactose monohydrate or microcrystalline cellulose, one or more disintegrators, each of them being independently selected from a pre-gelled starch or cross-linked sodium carboxymethyl cellulose, a binder and a lubricant. Still other preferable, but not exclusive, embodiments comprise a binder that is polyvynilpyrrolidone and lubricant that is a magnesium salt of silicic acid. Yet other preferable embodiments comprise a diluent that is lactose monohydrate, a disintegrator that is selected from a group and is sodium cross-carmellose, and a binder is povidone.

Adjuvants are selected for the purpose of delivering a corresponding amount of glutaryl histamine in a formulation made industrially. All adjuvants are selected so as to be inert, organoleptically acceptable and compatible with glutaryl histamine. Adjuvants that are used in solid preparative forms for oral administration include, as a rule, excipients or diluents, binders, disintegrators, lubricants, anti-adhesive agents, sliding agents, wetting agents and surfactants, pigments, flavoring agents, sweeteners, adsorbents and agents improving organoleptic properties.

Excipients or diluents are added to an active substance in order to increase a tablet volume. They include lactose that may be either crystalline or

amorphous. Various types of lactose include lactose monohydrate, α-lactose monohydrate, such as anhydrous forms of lactose (α-, β-) and agglomerated lactose. Other diluents include sugars, such as sugar derivatives. And one of the most common excipients is lactose monohydrate. Microcrystalline cellulose and cellulose microparticles are also used.

Starches and starch derivatives are also referred to as diluents and excipients.

Other starches include a pre-gelled starch or a starch modified with sodium glycolate. Starches and starch derivatives may be used as disintegrators also. Other diluents include nonorganic salts, such as dibasic calcium phosphate, tribasic calcium phosphate and calcium sulfate. As diluents, polyols may be used, such as mannitol, sorbitol and xylite. Many diluents also act as disintegrators and binders; and these additional properties should be taken into account while developing the formulation. Disintegrators are included into tableted formulations in order tablets may disintegrate into particles of an active pharmaceutical component and adjuvants, which would facilitate dissolution of an active component and improve its bioavailability. A pre-gelled starch may be a disintegrator. Cross-linked sodium carboxymethyl cellulose is another disintegrator. Disintegrators also include cross-linked polyvinylpyrrolidone (e.g., cross-povidone) and microcrystalline cellulose.

Binders are used for wet granulation. The function of a binder is to make a powder loose and facilitate pressing. Binders are cellulose derivatives, such as microcrystalline cellulose, methylcellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Other binders are polyvidone, polyvinylpyrrolidone, gelatin, natural gummies, e.g., acacia, tragacanth, guar and pectine gums, starch paste, a pre-gelled starch, sucrose, corn syrup, polyethylene glycols and sodium alginate,

ammonium calcium alginate, magnesium aluminum silicate, polyethylene glycols. A preferable, but not exclusive, binder is polyvinylpyrrolidone, in particular povidone.

Lubricants are used in tableted preparative forms for preventing a tablet from adhering to an impact surface and for reducing friction at pressing steps. Lubricantsusually include vegetable oils, e.g., corn oil, mineral oils, PEG polyethylene glycols, salts of stearic acid, such as calcium stearate, magnesium stearate and sodium stearyl fumarate, mineral salts, for example talc, non-organic salts, such as sodium chloride, organic salts, such as sodium benzoate, sodium acetate and sodium oleate, and polyvinyl alcohols. A preferable lubricant in the industrial use is magnesium stearate.

Sliding agents are used in solid formulations for improving fluidity of a tablet mass. Usually, such agents as microcrystalline cellulose; alkali-metal stearates, e.g., magnesium stearate or calcium stearate; silicate salts, e.g., magnesium silicate, calcium silicate; starch and its varieties and/or derivatives; talc; colloid silicon dioxide, for example, a well-known Aerosil®.

According to some embodiments, the glutaril histamine content is in the range from about 30% to about 50% of the composition weight. This composition comprises a diluent that is lactose monohydrate as well as microcrystalline cellulose is selected as a diluent, a pre-gelled starch is selected as a disintegrator; cross-linked carboxymethyl cellulose is selected as a second disintegrator, polyvinylpyrrolidone is selected as the binder, and magnesium stearate is selected as the lubricant.

According to another embodiment, a lactose monohydrate content is in the range from about 25% to about 40%, a microcrystalline cellulose content is in the range from about 5% to about 15%, a pre-gelled starch content if in the range from about 5% to about 15%, a cross-linked sodium carboxymethyl

cellulose content is in the range from about 1% to about 10%, a polyvinylpyrrolidone content is in the range from about 1% to about 10%, and a magnesium stearate content is in the range from about 0.2 to about 2.0%.

According to still further embodiment, a glutaril histamine content is about 40.0% of the composition weight, a lactose monohydrate content is about 30%, a microcrystalline cellulose content is about 10.5%, a pre-gelled starch content is about 11%, a cross-carmellose content is about 4.0%, a povidone content is about 5.5%, and a magnesium stearate content is about 0.5%. According to yet other embodiments, a glutaril histamine content is up to 80% (70-80%) of the composition weight. The composition may further comprise lactose in an amount of 2.5-20% of the composition weight; a disintegrator, namely, cross-linked carboxymethyl cellulose, in an amount of 1-10% of the composition weight; a binder selected, for example, as polyvinylpyrrolidone, in an amount of 2-10% of the composition weight; and a lubricant selected from a stearate group, e.g., magnesium (potassium) stearate, in an amount of 0.2-2.0% of the composition weight.

According to still other embodiments of this invention, lactose monohydrate is selected as the diluent, sodium cross-carmellose is selected as the disintegrator, povidone is selected as the binder, and magnesium, stearate is selected as the lubricant.

According to yet other embodiments, a glutaril histamine content is up to 80% of the composition weight, lactose monohydrate is selected as the diluent, its content being in the range from 8% to 15% of the composition weight; cross-linked sodium carboxymethyl cellulose in an amount of 1-10% of the composition weight is selected as the disintegrator; polyvinylpyrrolidone with a content of 1-10% of the composition weight is a binder; magnesium stearate is another binder with a content of 0.2-2.0% of the composition weight. According

to a more preferable embodiment, lactose monohydrate is selected as the diluent with the content of 9.5% of the composition weight, sodium cross-carmellose is selected as the disintegrator and amounts to 5% of the composition weight, the binder is povidone with the content of 5% of the composition weight, magnesium stearate is the lubricant in the amount of 0.5% of the composition weight. According to still further embodiments, glutaril histamine is about 90% of the composition weight. Preferably, but not exclusively, this composition also comprises a diluent, e.g., lactose monohydrate, preferably in an amount of 3-10% of the composition weight; a disintegrator, such as cross-linked carboxymethyl cellulose, in an amount of 2-5% of the composition weight; a binder, such as polyvinylpyrrolidone, in an amount of 2-5% of the composition weight; a lubricant, such as magnesium stearate, in an amount of 0.2-2.0% of the composition weight. According to other preferable embodiments, lactose monohydrate in the amount of 3.5% of the composition weight is selected as the diluent, sodium cross-carmellose in an amount about 3% of the composition weight is selected as the disintegrator, povidone in the amount of about 3% of the composition weight is selected as the binder, and magnesium stearate in the amount of about 1% of the composition weight is selected as the lubricant.

According to another embodiment of this invention a glutaril histamine composition in the amount of 90 mg is proposed, wherein a glutaril histamine content is 40-90% of the composition weight. According to still another embodiment a composition comprises glutaril histamine in an amount of 60-90% or 70-80%. According to yet another embodiment, these compositions may comprise one and/or more of starches, such as corn starch, pre-gelled starch, a cross-linked sodium salt of starch carboxymethyl ester, lactose monohydrate, microcrystalline cellulose, cross-linked sodium carboxymethyl cellulose; hydroxypropylmethyl cellulose; polyvinylpyrrolidone, a silicate salt,

e.g., magnesium silicate; a stearic acid salt, e.g., potassium stearate, and a mineral compound, such as talc.

According to the embodiments, these compositions comprise, preferably, but not exclusively, one standard dose of glutaryl histamine. Preferably, the standard dose is in the form of a solid formulation, such as a tablet or a capsule, and, more preferably, is a tablet. In particular, this tablet may comprise 30, 60, 100 and, preferably, 90 mg of glutaryl histamine in a solid formulation of 250 mg.

According to an industrial embodiment of this invention, a method is provided for producing a solid formulation of glutaril histamine by wet mixing of glutaril histamine and adjuvants with water, granulation, drying and comminution of a granulated mixture. According to one of the embodiments, a final mixture is pressed for producing tablets. According to other embodiments, a final mixture is encapsulated. The method includes the steps of: dry mixing of glutaril histamine and one or more adjuvants for producing a dry mixture; wetting of the dry mixture with prepared water for producing a wet granulation mixture; drying for producing a dry granulation mixture; comminution for producing a comminuted granulation mixture; mixing of the comminuted granulation mixture with a lubricant for producing a final mixture; production of a solid formulation for oral use from the final mixture. According to some preferable embodiments, a final mixture is pressed for producing tablets. According to other preferable embodiments, a final mixture is encapsulated.

Best Mode for Carrying Out the Invention

Example 1.

Preparation of glutaril histamine 100 mg tablets

Production of dry granulated material

Table 1.

Spent in the step (in total)

Names of semi-products and stock	***Spent weight, kg***	
	Minimum run	***Maximum run***
1	***2***	***3***
A. Semi-products:		
Glutaril histamine, sifted, 100 %, per run per batch	 **3.000** -	 **23.252** 7.751
Dry sifted potato starch per run per batch	 **1.414** -	 **10.956** 3.652
Lactose (milk sugar), sifted per run per batch	 **4.193** -	 **32.495** 10.832
5% starch paste per run per batch	 **2.028** -	 **15.720** 5.240
In total:	**10.635**	**82.423**

Produced in the step (in total)

Table 2.

Names of semi-products and stock	***Produced weight, kg***	
	Minimum run	***Maximum run***
1	***2***	***3***
A. Semi-products:		
Dry granulated material, including*	8.534	66.139
Glutaril histamine	*2.700*	*22.787*
B. Waste:		
Sweepings from equipment, including	0.087	0.675

Glutaril histamine	*0.150*	*0.233*
C. Losses:		
Into industrial sewer, including	0.058	0.450
Glutaril histamine	*0.100*	*0.155*
Into the environment, including	0.029	0.225
Glutaril histamine	*0.050*	*0.077*
Moisture loss	1.927	14.934
In total:	**10.635**	**82.423**

Production of wet granulated material

Sifted glutaril histamine, 100 % – 3.000 (7.751) kg, dry sifted potato starch – 1.414 (3.652) kg, sifted lactose (milk sugar) – 4.193 (10.832) kg, 5 % starch paste – 2.028 (5.240) kg are weighed to production containers.

Sifted glutaril histamine, dry sifted potato starch, sifted lactose (milk sugar) are fed to high-speed mixer-granulator, e.g. GHL-250 GF-335 (for a minimum run: to a production container GF-201) and mixed for 3-5 minutes. Then, 5% starch paste is added and mixed for 20-30 seconds (for a minimum run: 2-3 minutes), until a uniformly wet mass is produced. The mass, when pressed in the hand, should clump easily, and should disintegrate at a light stroke.

The wetted mass is fed to the drying step.

Drying and dry granulation

The wetted mixture is dried in the granulator in the FL-60 fluidized layer SSH-337 at the temperature of 45±5°C for 20-45 minutes until the residual moisture content is 2.0-3.0% (Sartorius moisture analyzer at 100°C) or, for a minimum run: the wetted mixture is dried in the air, on trays for 10-12 hours). Before determining the moisture content with the use of Sartorius moisture analyzer, a sample of the dried mass is to be granulated for the purpose of obtaining more accurate measurement.

The dried mixture is discharged into production containers and passed

through an universal granulator GR-1 GF-332 having a drum hole diameter of 1.0-1.5 mm (for a minimum run: through a hand sieve GF-210 having the hole diameter of 1,000 microns in a dry box VSH-208 (1)) and collected in production containers (KT-3; TP-3.2).

The glutaril histamine output at this step is 90.00 (98.00) %.

A deviation from the regulation output (98,00±0,50) % is allowed: (65.808-66.470) kg or (90.00±0.50) %: (8.491-8.577) kg of dry granulated material.

Production of glutaril histamine 100 mg tablets

Preparation of tablet mass

Dry granulated material – 8.534 (22.046) kg, ground and sifted stearic acid – 0.081 (0.228) kg, sifted magnesium stearate – 0.081 (0.228) kg, calcined and sifted talc – 0.081 (0.228) kg, sifted colloid silicon dioxide (Aerosil) – 0.020 (0.057) kg, ground offgrade tablets and siftings – 0.025 (0.107) kg are weighed and fed into production containers GF-201, GF-302 (KT-1, TP-4.1).

Dry granulated material, sifted colloid silicon dioxide (Aerosil), ground offgrade tablets and siftings are fed to a dragee pan DR-5 GF-340 (for a minimum run: to a production container GF-201) and mixed for 1-2 minutes. Then, sifted magnesium stearate, calcined and sifted talc, ground and sifted stearic acid are added and mixed for 2-3 minutes (KT-2; TP-4.1).

This tablet mass is averaged in the dragee pan DR-5 GF-340 for 3-5 minutes, a tablet mass sample is analyzed for glutaril histamine content, and, if satisfactory results are obtained, the tablet mass is fed to the tableting step (KT-3, TP-4.1).

Tableting and rejection

Tableting is carried out in a rotary pressing machine MRC-30N GF-230 having the punch diameter of 9 mm. Tablets should have white color or white

color with cream tint, the shape of flat cylinder with a bevel and a notch, unbroken edges, smooth and uniform surface and should not have cracks or cleavages.

Before starting tableting, the rotary pressing machine MRC-30N GF-230 is provided with a tag indicating the preparation name, the run number, the tablet weight. Tablet mass is fed to the hopper of the pressing machine, and tableting starts. Addition of the tablet mass and dust removal are carried out automatically. During tableting, tablet average weights, any deviation from a tablet average weight, description, firmness are checked.

Offgrade tablets are rejected, collected in GF-201 containers and fed to a universal granulator GR-1 GF-332 for grinding. Tablets of standard condition are held for relaxing stresses arising inside tablets due to a high pressure developed by the pressing machine for 6-8 hours.

Example 2.

Production of dry granulated material

Table 3.

Spent in the step (in total)

Names of semi-products and stock	***Spent weight, kg***			
	Dose 30 mg		***Dose 90 mg***	
	Minimum run	***Maximum run***	***Minimum run***	***Maximum run***
1	***2***	***3***	***4***	***5***
A. Semi-products:				
Sifted glutaril histamine , 100 %, per run	4.066	16.264	9.785	39.140
per batch	-	4.066	-	9.785

Sifted lactose, per run per batch	13.594 -	54.376 13.594	9.839 -	39.357 9.839
Dry sifted potato starch, per run per batch	5.970 -	23.880 5.970	3.561 -	14.245 3.561
5 % starch paste, per run per batch	4.480 -	17.900 4.480	5.100 -	20.400 5.100
In total:	**28.110**	**112.420**	**28.285**	**113.142**

Table 4.

Produced in the step (in total)

Names of semi-products and stock	***Produced weight, kg***			
	Dose 30 mg		***Dose 90 mg***	
	Minimum run	***Maximum run***	***Minimum run***	***Maximum run***
1	***2***	***3***	***4***	***5***
A. Semi-products:				
Dry granulated material, including*	23.341	93.364	22.937	91.746
Glutaril histamine	*3.979*	*15.915*	*9.574*	*38.297*
B. Waste:				
Sweepings from equipment, including	0.257	1.026	0.252	1.008
Glutaril histamine	*0.044*	*0.175*	*0.106*	*0.422*
C. Losses:				
Into industrial sewer, including	0.171	0.684	0.168	0.672
Glutaril histamine	*0.029*	*0.116*	*0.070*	*0.281*
Into the environment, including	0.085	0.341	0.083	0.336
Glutaril histamine	*0.014*	*0.058*	*0.035*	*0.140*
Moisture loss	4.256	17.005	4.845	19.380

Names of semi-products and stock	Produced weight, kg			
	Dose 30 mg		Dose 90 mg	
	Minimum run	Maximum run	Minimum run	Maximum run
1	2	3	4	5
In total:	28.110	112.420	28.285	113.142

Production of wet granulated material

Sifted glutaril histamine, 100 % – 4.066 (9.785) kg, dry sifted potato starch – 5.970 (3.561) kg, sifted lactose – 13.594 (9.839) kg, 5 % starch paste – 4.480 (5.100) kg are weighed to production containers GF-201, 302. (KT1, TP-3.1)

Sifted lactose, dry sifted potato starch, sifted glutaril histamine are fed to high-speed mixer-granulator GHL-250 GF-222 and mixed for 3-5 minutes. Then, 5% starch paste is added and mixed for 20-30 seconds, until a uniformly wet mass is produced. The mass, when pressed in the hand, should clump easily, and should disintegrate at a light stroke (KT-2, TP-3.1)

The wetted mass is collected in production containers GF-201, 302 and fed to the drying step TP-3.2.

Drying and dry granulation

The wetted mixture is dried in the drier-granulator SG-30m SSH-219 in the FL-60 fluidized layer GF-337 at the temperature of 55±5°C for 40-60 minutes until the residual moisture content is 2.0-3.0%. Before determining the moisture content with the use of Sartorius moisture analyzer, a sample of the dried mass is to be granulated for the purpose of obtaining more accurate measurement.

The dried mixture is discharged into production containers GF-201, GF-302 and passed through an universal granulator GR-1 GF-218 (2), GF-332 (2) having a drum hole diameter of 1.0-1.5 mm and collected in production containers (KT-3; TP-3.2).

The dry granulated material is passed to the step of producing a mixture for encapsulating TP-4.1.

Encapsulation

Encapsulation is carried out in a capsule filler MG Compact GF-237, a capsule filler NJP-800C GF-338, a capsule filler SF-100N GF-.

A mixture for encapsulation is fed into the hopper 1 of a capsule filler, solid gelatin capsules are fed into the hopper 2, and encapsulation starts. The mixture for encapsulation is added automatically, when the hoppers are empty.

The objective of the invention is to expand the range of agents exhibiting virus-tropic and immunogenic activity.

This objective is achieved by the new pharmaceutical composition in a solid drug formulation, which exhibits virus-tropic and immunogenic activity and is characterized in that it comprises, as the active substance, glutaryl histamine in an amount up to 94 weight % and adjuvants form the rest. According to the most preferable embodiment, the glutaril histamine content may be in the range from 80 to 94 weight %. This formulation may comprise, as adjuvants, lactose monohydrate, microcrystalline cellulose, sodium cross-carmellose, colloid silicon dioxide (Aerosil 300) and calcium stearate. Such high content of the active substance is not disclosed in the state of the art.

A particular case of the new pharmaceutical composition in the tablet form exhibiting virus-tropic and immunogenic activity is its formulation characterized in that it comprises glutaryl histamine as the active substance and lactose monohydrate, microcrystalline cellulose, sodium cross-carmellose, colloid silicon dioxide (Aerosil 300) and calcium stearate as adjuvants, the said ingredients having the following content, in weight per cent:

Glutaryl histamine	18.0-75

Microcrystalline cellulose	18.0-71
Sodium cross-carmellose	0.25-1
Colloid silicon dioxide (Aerosil 300)	0.5-2
Calcium stearate	0.5-2
Lactose monohydrate	the rest.

In order to further raise the composition stability, the active substance is first dried to a moisture content not more than 1.5%.

Embodiments of the Invention

Example A. Composition

Active substance:	
glutaryl histamine	30.00 mg
Adjuvants:	
lactose monohydrate (BP/Eur.Ph. or USP-NF)	34.00 mg
monocrystalline cellulose (BP/Eur.Ph. or USP-NF)	47.62 mg
sodium cross-carmellose (BP/Eur.Ph. or USP-NF)	0.68 mg
Aerosil 300 (GOST 14922-77 or BP/Eur.Ph. or USP-NF)	1.35 mg
calcium stearate (BP/Eur.Ph. or USP-NF)	1.35 mg
Tablet weight	135.00 mg

Example B. Composition.

Active substance:	
glutaryl histamine	100.00 mg
Adjuvants:	

lactose monohydrate (BP/Eur.Ph. or USP-NF)	68.00 mg
monocrystalline cellulose (BP/Eur.Ph. or USP-NF)	95.25 mg
sodium cross-carmellose (BP/Eur.Ph. or USP-NF)	1.35 mg
colloid silicon dioxide (Aerosil) (GOST 14922-77 or BP/Eur.Ph. or USP-NF)	2.70 mg
calcium stearate (BP/Eur.Ph. or USP-NF)	2.70 mg
Tablet weight	270.00 mg

Values of the pharmacokinetic parameters did not show any essential deviations during the study.

The elimination rate constant is 0.22±0.004.

The absorption rate constant is 1.695±0.028.

Time of reaching a maximum concentration, Tmax, hours, is 1.3±0.1.

The maximum concentration, Cmax, μg/mL, is 70.3±2.0

Example **3**. Studies of the formulation

3.1. Toxicological studies (Tables 5, 6).

The toxicological study results

According to data on acute and chronic toxicity, the glutaril histamine composition may be referred to a relatively harmless preparation.

1. The composition does not exhibit allergenic and mutagenic properties.
2. The glutaril histamine composition does not exhibit reproductive toxicity.
3. The composition in all the doses studied (0.05, 0.5, 5.0 mg/kg of glutaril histamine) does not exhibit carcinogenic activity that was shown in the conditions of a 24-month experiment.

Table 5.

Kind of study	Types of animals	Method of introduction	Doses	Period of observation
Acute toxicity of the substance	Rats, mice	Orally, intraperitoneally	Up to 3,000 mg/kg	14 days
Chronic toxicity of the substance	Rats	Orally, intraperitoneally	2,5 and 25 mg/kg	6 months
	Dogs	Orally	2,5 mg/kg	3 months
Acute toxicity of the final formulation	Mice	Orally	150, 300, 450, 600 and 750 mg	14 days
Sub-acute toxicity of the final formulation	Rabbits	Orally	12 and 36 mg/kg	1 month

Table 6.

Kind of study	Types of animals	Doses studied	Type of study
Allergenicity	Cavies,	500, 5000 µg/kg	in vivo
	Non-linear mice (n=12)	11.5 mg/kg	in vivo
Reproductive toxicity	Rats of both genders	2.5 and 25 mg/kg	in vivo
Mutagenicity	Mice	12.5 mg/kg	in vivo
	Ames test	1.0, 10.0, 100, 1000, and 10000 µg /mL	in vitro
Carcinogenicity	Rats and mice	0.05, 0.5, 5.0 mg/kg	in vivo

2. Study of the glutariyl histamine composition efficiency in relation to an A-influenza agent and adenoviruses in experiments in vitro and in vivo.

Materials and methods:

The following materials were used for the in vitro studies:

- A/Aichi/2/68 (H3N2) and A/hen/Kurgan/Russia/2/05 (H5N1) strains;

- GMK-AH-1 constant cultures of green-monkey kidney cells, MDCK dog kidneys;

- PS-4 growth semi-synthetic medium.

The following materials were used for the studies in vivo:

- white outbred mice having the weight of 15 g that are obtained from the vivarium of VTs NIIM, Moscow Region, Russia.

The laboratory animals were infected intranasally.

During the studies in vitro at the infective dose of 0.1 of a cytopathic dose 50/cell the glutaryl histamine composition in a concentration of 100-200 μg/mL efficiently suppresses the reproduction of the influenza virus A (strain A/Aichi/2/68 (H3N2) и A/hen/Kurgan/Russia/2/05 (H5N1)) when delivered in 2 hours after infecting a mono-layer.

During the studies in vivo the glutaryl histamine composition at the dose of 5 mg/kg is efficient as a prophylactic drug in relation to the influenza A (H3N2 and H5N1).

The prophylactic efficiency of the glutaryl histamine composition is slightly inferior in comparison to Tamiflu.

When used according to the urgent prophylaxis system and for treatment, the glutaryl histamine composition is inferior in comparison with Tamiflu. The optimal dose of the glutaryl histamine composition according to the said system is 15 mg/kg.

3.3. A study of interferon-inducing and immunomodulating activity of the glutaryl histamine composition:

- preparation and doses: glutaryl histamine composition, oral introduction;

- material for the study: blood samples of 15 healthy rats before and after introduction of the preparation;

materials and methods:

indices of the IFN-status were monitored in 2, 4, 6, 8, 12, 24, 48 hours after the introduction of the preparation.

3.3.1. The results of the study of interferon-inducing and immunomodulating activity of the glutaryl histamine composition:

single oral introduction raises the interferon content by 73.3% of the donors within the upper limits of the physiological norm in 24-48 hours;

the composition stimulates and normalizes a lowered α-IFN-producing ability of leucocytes in practically healthy animals in 24 hours;

single introduction of the glutaryl histamine composition stimulates the γ-IFN production.

Thus, the new composition has showed high results of pharmacological activity and may be recommended for the introduction into the clinical practice.

Industrial Applicability

The invention is applicable in the field of medicine, the chemical-pharmaceutical industry, namely for the production of agents exhibiting nootropic and neuromodulating activity, and relates to new glutaryl histamine compositions and methods for making same.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition in a solid formulation exhibiting virus-tropic and immunogenic activity, characterized in that it comprises glutaryl histamine as the active substance, lactose monohydrate, microcrystalline cellulose, sodium cross-carmellose, colloid silicon dioxide (Aerosil 300) and calcium stearate as adjuvants, the ingredients having the following contents, in weight per cent:

Glutaril histamine	18.0-94
Adjuvants	the rest.

2. A pharmaceutical composition according to Claim 1, characterized in that it comprises glutaril histamine in an amount of 92-94% weight per cent.

3. A pharmaceutical composition according to Claim 1, characterized in that it comprises glutaril histamine as the active substance, and lactose monohydrate, microcrystalline cellulose, sodium cross-carmellose, colloid silicon dioxide (Aerosil 300) and calcium stearate as adjuvants, the ingredients having the following contents, in weight per cent:glutaryl histamine 18.0-75.0

monocrystalline cellulose	18.0-71.0
sodium cross-carmellose	0.25-1.0
colloid silicon dioxide (Aerosil 300)	0.5-2.0calcium stearate 0.5-2.0
lactose monohydrate	the rest.

4. The pharmaceutical composition according to Claim 1, characterized in that the active substance is first dried to moisture content not more than 1.5%.

5. A method for producing a pharmaceutical composition according to any of Claims 1-2, characterized in that sifted powder of microcrystalline cellulose is thoroughly mixed for 1÷2 minutes; sifted powder of glutaryl

histamine and sifted lactose monohydrate are added, and the obtained mixture is thoroughly mixed for 5÷7 minutes; then sifted powder of sodium cross-carmellose is added, and the obtained mixture is mixed for 3÷5 minutes; sifted powders of colloid silicon dioxide and calcium stearate are added, and the obtained mixture is again mixed for 2÷4 minutes; and the thus produced mixture is tableted by direct pressing.

6. A method for producing a pharmaceutical composition according to any of Claims 1-4, characterized in that the glutaril histamine composition is made as a capsule.