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(54) **Title**: COMPOSITION FOR PREVENTING HEADACHES

(57) **Abstract**: The present invention concerns a non-toxic solid pharmaceutical composition for oral administration, containing one or more cysteine compounds from the group of L-cysteine, D-cysteine and N-acetyl cysteine, combined with one or more additional active agents, at least one of which being selected from cystine, glutathione and methionine, the composition further containing one or more pharmaceutical additives. Further, the invention concerns a method for reducing the incidence of severe headaches, particularly migraine and/or cluster headaches.

COMPOSITION FOR PREVENTING HEADACHES

Field of the Invention

The present invention concerns a non-toxic oral pharmaceutical composition for reducing the incidence of, or preventing, or at least relieving, severe headaches, particularly migraines or cluster headaches. Further, the invention concerns a method for reducing the incidence of, or preventing such severe headaches.

Description of Related Art

Cluster headache is a neurological disease that involves, as its most prominent feature, excruciating unilateral headaches of extreme intensity. "Cluster" refers to the tendency of these headaches to occur periodically, with active periods interrupted by spontaneous remissions. The cause of the disease is currently unknown. It affects approximately 0.1% of the population.

While migraines are diagnosed more often in women, cluster headaches are more prevalent in men. The male-to-female ratio in cluster headache is about 5:1. It primarily occurs between the ages of 20 to 50 years.

In Finland alone, over 15 000 people suffer from Cluster Headaches (about 0.3 % of the population). The number of people suffering from migraine is even larger (10 to 20 % of the population).

The duration of the common attack ranges from as short as 15 minutes to three hours or more. If untreated, the attack frequency is from 1 to 16 attacks in 48 hours. The headache may be accompanied by one or more of the following autonomic symptoms: ptosis (drooping eyelid), miosis (pupil constriction), conjunctival injection (redness of the conjunctiva), lacrimation (tearing), rhinorrhea (runny nose), and, less commonly, facial blushing, swelling, or sweating, all appearing on the same side of the head as the pain.

The onset of an attack is rapid, and most often without the preliminary signs that are characteristic of a migraine.

Cluster headaches are occasionally referred to as "alarm clock headaches" because of their ability to wake a person from sleep and because of the regularity of their timing: both the individual attacks and the clusters themselves can have a metronomic regularity; attacks striking at a precise time of day each morning or night is typical, even precisely at the same time a week later. The clusters tend to follow daylight saving time changes and happen more often in spring and fall equinox. This has prompted researchers to speculate an involvement of the brain's "biological clock" or circadian rhythm.

In episodic cluster headaches, the attacks occur once or more often daily, often at the same times each day, for a period of several weeks, or even months, followed by a headache-free period lasting weeks, months, or years. These episodes often occur during the same season, e.g. during the autumn or the spring.

However, approximately 10–15% of cluster headache sufferers are chronic, and they can experience multiple headaches every day for years. About 10% of episodic cluster headaches turn into the chronic type at some point in time.

Cluster headaches are sometimes classified as vascular headaches. The intense pain has been suggested to be linked with the dilation of blood vessels which creates pressure on the trigeminal nerve. While this process is seen as the immediate cause of the pain, the etiology is not fully understood.

The episodes are known to be triggered by factors, such as alcohol consumption, changes in sleeping habits, excess physical strain, outbursts of anger and pressure variations (e.g. during flights or mountain climbs). A link has also been implied between these episodes and smoking.

The last mentioned affliction is often found in people with a heavy addiction to cigarette smoking. There are also cases where second hand smoke has been shown to trigger cluster headaches.

Sensitivity to alcohol during a cluster bout also occurs. Patients who are sensitive to alcohol note that attacks are triggered within 5 to 45 minutes after the ingestion of modest

amounts of alcohol, usually being less than a single cocktail or glass of wine. Alcohol triggers attacks in 70 to 80 % of exposures.

Experimentally, attacks can be triggered in nearly all patients during a bout by the administration of nitroglycerin or histamine. Histamine most likely functions by triggering an inflammatory response.

It has also been shown that mast cells, the major repository of histamine in many tissues, are found in increased number in the skin of the painful temporal area in cluster headache patients. This effect is also found in migraine patients.

Cluster headaches are benign, but because of the extreme and debilitating pain associated with them, and potential risk of suicide, a severe attack is nevertheless treated as a medical emergency. Because of the relative rareness of the condition and ambiguity of the symptoms, some sufferers may not receive treatment in the emergency room and people may even be mistaken as exhibiting drug-seeking behavior.

There are other types of headache that are sometimes mistaken for cluster headaches, such as Chronic Paroxysmal Hemicrania (CPH) and ictal headache.

Medications to treat cluster headaches are classified as either abortive (e.g. cortisone, migraine medicines, ergotamine tartrate, naratriptan, frovatriptan or a local anesthetic to the occipital nerve) or prophylactics (preventatives, e.g. verapamil, lithium, sodium valproate, topiramate, baclofen, melatonin, methysergide, indomethacin or capsaicin). In addition, short-term transitional medications (such as steroids) may be used while prophylactic treatment is instituted and adjusted.

European guidelines suggest the use of the calcium channel blocker verapamil. Steroids, such as prednisolone/prednisone, are also used. Methysergide, lithium and the anticonvulsant topiramate are recommended as alternative treatments.

Over-the-counter pain medications (such as aspirin, paracetamol, and ibuprofen) typically have no effect on the pain from a cluster headache. The treatment is generally selected

based on the individual's experience, after testing various medications. No reliable test results have been available.

However, the present inventors have surprisingly found that a pharmaceutical composition decreasing the amount of acetaldehyde carried to or formed in the body of a human subject will alleviate and prevent these severe headaches, particularly cluster headaches, which could provide a link between these headaches and said alcohol consumption as well as smoking.

The first metabolite of alcohol is acetaldehyde. The alcohol is evenly distributed in the liquid phase of the organs. Hence, after enjoying alcohol and as long as there is alcohol in the organs, the alcohol content in the blood, saliva, gastric juice and the contents of the intestine is the same. The acetaldehyde is formed from the alcohol, among others, through microbial action. Microbes, among others in the digestive tract, are capable of oxidizing alcohol to acetaldehyde. For example, even after a moderate dose of ethanol (0.5 g/kg), high acetaldehyde contents of a microbial origin (18 – 143 μM) have been found in human saliva. In other words, acetaldehyde builds up in the saliva as an intermediate product of the microbial metabolism (Homann et al, Carcinogenesis (1997) 18:1739 – 1743).

In the organism, acetaldehyde is thus formed from alcohol as a consequence of the hepatic metabolism and, locally, in the digestive tract via microbial alcohol dehydrogenase (Salaspuro et al, (1996) Ann Med 28:195 – 200). The saliva spreads from the mouth to the other areas of the digestive tract, whereby areas of influence of the acetaldehyde contained in the saliva include the mouth, the pharynx, the oesophagus and the stomach. Consequently, the effects of acetaldehyde may extend to the whole upper digestive tract area.

It has also been shown that acetaldehyde builds up in the large intestine, as its bacteria that represent the normal flora are capable of converting ethanol into acetaldehyde (Jokelainen et al, (1996) Gut 39:100 – 104). In the intestines, endogenous ethanol can also be found, i.e. ethanol that is formed in the intestines in oxygen-free conditions under the effect of microbes. Acetaldehyde is formed, when this ethanol comes into contact with oxygen near the mucous membrane, for example.

On the other hand, carcinogenic acetaldehyde can be produced also endogenously by the oral microbes from various foodstuffs with high sugar or carbohydrate content, which will cause an increased acetaldehyde-content also in the stomach, especially in subjects suffering from an achlorhydric stomach.

Our recent studies have shown that all sugar (saccharose, maltose, lactose) -containing foodstuffs including beverages, can contain significant amounts of acetaldehyde, 5 to 2000 μM and ethanol, 0.1 to 0.5 per mille, or the acetaldehyde can be formed in the foodstuff. Some sour milks, yoghurts and juices contain acetaldehyde and ethanol, as such (PCT/FI2006/000104 incorporated herein by reference).

During active smoking, the acetaldehyde in the saliva was also increased to a value of 261.4±45.5 μM from the basic level (Salaspuro et al. (2004) Int J Cancer, 2004 Sep 10; 111(4):480 – 3).

The prior art discloses pharmaceutical compositions which contain compounds that bind acetaldehyde, their effect being based on the reaction of the effective substances with the acetaldehyde inside blood and/or cells, for example, US 5 202 354, US 4 496 548, US 4 528 295, US 5 922 346.

When such a composition is swallowed, the effective substances are instantly taken to the small intestine and from there into the blood circulation (Matsuoka, US Pat No 5,202,354 and Moldowan et al, US Pat No 4,496,548).

Suggestions have been made so as to use preparations containing amino acids and vitamins, which are sucked or chewed in the mouth, to reduce the liver-mediated effect of detrimental free-radical compounds, which are formed when using tobacco products or being exposed to the same. It is believed that, after being absorbed, amino acids affect various tissues (Hersch, US Pat No 5,922,346, Hersch, International Patent Application WO 99/00106). However, in all these cases, the effect is merely systemic.

Publication WO 02/36098 (incorporated herein by reference) suggests the use of a compound containing a free sulphhydryl and/or amino group for a local and long-term binding of acetaldehyde from saliva, the stomach or the large intestine. The compound was

mixed with a substance that enabled it to be released for at least 30 minutes in the conditions of the mouth, the stomach or the large intestine. In this case, the effect is limited to the gastrointestinal tract.

Publication WO 2006/037848 (incorporated herein by reference) suggests a composition comprising a compound containing one or more free sulphhydryl and/or amino group for removing or decreasing the aldehyde content of the saliva during smoking. Also this effect is only local.

However, none of the prior art suggests using cysteine or cystine or other similar compounds to relieve or prevent any types of headache. Further, no combination products have been developed.

Based on our recent studies, acetaldehyde plays a part in causing severe headaches, particularly cluster headaches and migraines. Since these conditions cannot yet be effectively prevented, and all existing prophylactic medicines have severe side effects, there is thus a need to find alternative and mild ways to at least relieve the symptoms or reduce the number of episodes in subjects suffering from these severe headaches.

Summary of the Invention

It is an aim of the present invention to provide new compositions, which can be used to prevent or at least reduce the incidence of episodes of severe headaches, such as cluster headaches, migraine, ictal headache or chronic paroxysmal hemicrania.

It is also an aim of the present invention to provide new methods and uses for treating people diagnosed to suffer from cluster headaches or migraine.

Particularly, it is an aim of the invention to provide compositions, which can be used in the treatment or prevention of severe headaches, and which mask the taste of the active agents.

These and other objects, together with the advantages thereof over known products and methods, are achieved by the present invention, as hereinafter described and claimed.

Compositions containing one or more cysteines as active agents have been shown to bind acetaldehyde. These active agents have been found to also be capable of breaking down biofilms formed by some microbes, particularly in the stomach. Also at least a partial eradication of microbes can be accomplished using a composition containing a cysteine, although this effect might be a result of the destruction of the biofilms, whereby the stomach acids are able to attack the microbes.

All the above mentioned effects of compositions containing one or more cysteines have been shown to be successful also in subjects having achlorhydria, or a low-acid stomach, often linked to *H. pylori* infections. To estimate the magnitude of the problems caused by acetaldehyde in the gastrointestinal tract (GI tract), it would be recommendable to start any treatment with a diagnosis as to the possible *H. pylori* infection.

The composition of the present invention can be used to prevent cluster headaches (CHA), regular migraines or both, or even ictal headaches or chronic paroxysmal hemicrania.

Thus, the present invention concerns a non-toxic solid pharmaceutical composition for oral administration, containing one or more agent from the group of L-cysteine, D-cysteine and N-acetyl cysteine, combined with one or more agent selected from cystine, glutathione and methionine.

More specifically, the composition of the present invention is characterized by what is stated in the characterizing part of Claim 1.

Further, the active agents of the invention for medical use according to the invention is characterized by what is stated in Claim 22, and the method of the present invention is characterized by what is stated in Claim 23.

Considerable advantages are obtained by means of the invention. Thus, the present invention provides a composition and method for preventing or at least decreasing the incidence or number of headache episodes in subjects suffering from severe headaches, such as cluster headaches or migraine.

The compositions are effective for releasing the active agents in a food product or drink (including water or any beverages), particularly in cases where these food products or drinks contain alcohol, acetaldehyde, yeast or sugars. Preferably, in these cases, the composition is added to the food product or the drink in connection with the consumption, i.e. eating or drinking. In practice, the composition is added to the food product or drink just before eating or drinking.

The compositions are also effective for releasing the active agents in the mouth or in the stomach, and binding acetaldehyde, in particular, when they are consumed in connection with eating or drinking, i.e. just before, during or just after eating or drinking, or in connection with smoking. In practice, the compositions are generally administered while the subject sits at the dining table, or immediately before lighting a cigarette (or beginning the use of another tobacco product) or immediately after putting the cigarette out.

However, despite the here implied local effect, the compositions also have a systemic effect, due to the additional active agent, selected from cystine, glutathione and methionine. This additional active agent is transformed into cysteine in the body, but said transformation mainly takes place after the agent has passed the stomach, whereby it will be transferred via the small intestine into the blood stream, to provide a wider area of action (via the systemic route), and a broader range for the effect.

The compositions can be used also in a continuous manner, for example after every 8 to 10 hours. The composition comprises one or more carriers that regulate the release of the active agents, thus giving a continuous effect.

Next, the invention will be described more closely with reference to the attached drawings and a detailed description.

Brief Description of the Drawings

Figure 1 demonstrates the effect of compositions containing cysteine in different amounts on the acetaldehyde levels of the saliva.

Figure 2 demonstrates the changes in the salivary acetaldehyde levels during smoking.

Figure 3 demonstrates the binding of the acetaldehyde formed during smoking using cysteine.

Figure 4 demonstrates the effect of a chewing gum containing L-cysteine (7.5 mg) on salivary acetaldehyde levels during smoking, as compared to the use of a placebo chewing gum.

Detailed Description of the Preferred Embodiments of the Invention

The present invention concerns a non-toxic solid pharmaceutical composition for oral administration, containing one or more cysteine compound from the group of L-cysteine, D-cysteine and N-acetyl cysteine as active agents, combined with one or more additional active agents, at least one of which being selected from cystine, glutathione and methionine, the composition being intended for reducing the incidence of, or even preventing severe headaches.

The term "cysteine compound" is intended to mean a cysteine, such as L- or D-cysteine, or a derivative or salt thereof, particularly N-acetyl cysteine. The function of this main active agent is based on the local effect obtainable through the reaction of this cysteine compound in the gastrointestinal tract.

The function of the mentioned additional active agent(s) selected from cystine, glutathione and methionine is based on the capability of these agents to be transformed into cysteine or to provide a similar effect as cysteine, although systemically.

The partially local and partially systemic effects are possible due to the different reactivities of these groups of active agents in the gastrointestinal tract. The main cysteine compound will react, particularly with the acetaldehyde, in the stomach, while the additional active agent selected from cystine, glutathione and methionine will be transferred, mainly via the small intestine, to the blood stream before reacting.

According to an embodiment of the invention, the composition further contains diamine oxidase (i.e. histaminase) as an active agent for degrading excess histamine.

According to a preferred embodiment, the active agents, however, consist of amino acids selected from L-cysteine, D-cysteine, N-acetyl cysteine, cystine, glutathione and methionine.

According to another embodiment, a vitamin or a similar nutritious supplement is further included in the composition. This supplementary agent can be, for example, a taurine compound or a common water-soluble vitamin, such as vitamin C, B_2 or B_5, due to the contents of reactive functional groups of these compounds, or a salt thereof. Preferably, the supplementary agent is vitamin C or a salt of taurine, such as a magnesium or calcium salt, due to the additional neuro-muscular activity of such salts. More preferably the supplementary agent is a magnesium taurinate, most suitably magnesium N-acetyl taurinate. These compounds have here been found to further reduce the incidence of, or even prevent severe headaches.

The composition may be formulated into, for example, a tablet, a capsule, a granule, or a powder, or optionally into a tablet or a capsule filled with said powder or granules. Thus, the composition may be formulated into a monolithic or multiparticular preparation. The composition for release in a foodstuff or a drink (including water and any beverages) is preferably formulated into and added to said foodstuff or drink in the form of a powder or granules. The composition for administration into and release in the mouth or the stomach of the subject, in turn, is preferably administered as a capsule, tablet or lozenge, most suitably as a capsule enclosing the active agents and additives in granulated form.

The function of the cysteine or the N-acetyl-cysteine is based on the neutralization of the acetaldehyde formed during smoking or during the consumption of alcohol, or of alcohol- or acetaldehyde-containing foodstuff or drinks, including foodstuff and drinks that contain materials that are capable of forming alcohol or acetaldehyde prior to or just after consumption, such as certain bacteria, yeasts or carbohydrates.

The above mentioned optional vitamins and supplements function by amplifying the acetaldehyde-binding effect of the cysteine compound.

The function of the cystine, the glutathione or the methionine is, in turn, based on its low reactivity in the gastrointestinal tract, whereby it is conducted directly to the small intestine

in its original form, where it will firstly be transformed into cysteine and react with any remains of acetaldehyde carried past the stomach, and secondly be carried to the blood stream and further on to the organs, particularly the liver, to eliminate any acetaldehyde formed in these organs.

The function of the diamine oxidase (i.e. histaminase) is based on its enzymatic activity in degrading histamine, whereby this further cause of severe headaches is reduced.

Definitions

The composition of the present invention comprises an effective amount of one or more agent from the group of L-cysteine, D-cysteine and N-acetyl cysteine, as well as of one or more agent selected from cystine, glutathione and methionine. The glutathione can be present in the composition in either oxidized or reduced form. Preferably, the reduced form is used, since this will provide an increased local effect, while the oxidized form can be targeted to the systemic route of action. Optionally, also an effective amount of diamine oxidase, a taurine compound or a common water-soluble vitamin can be included in the composition.

An "effective amount" means an amount capable of binding or inactivating an amount of acetaldehyde present in a foodstuff, alcohol, other drink or tobacco, or formed during the consumption of foodstuff, alcohol or other drink, or after eating or drinking, or formed during or after smoking, or at least keeping the acetaldehyde content essentially lower than without the use of the composition. In case of diamine oxidase, an effective amount means an amount capable of degrading an excess of histamine temporarily formed in the subject.

Keeping the acetaldehyde content essentially lower than without the use of the composition means that the acetaldehyde content should be kept at a level that is at least 20%, preferably over 40%, and most preferably over 60% lower than when not using the composition according to the description of the invention.

The mentioned acetaldehyde is mainly formed in the saliva of the subject. Due to the deposition of acetaldehyde into the aerodigestive tract, the acetaldehyde also reaches the esophagus and stomach via normal wash-out of saliva. Further, the alcohol reaching further

into the blood-stream will be spread throughout the body and into the organs, where it can cause harm as such, or can be transformed into acetaldehyde. Thus, the harm is, at least to a small extent, systemic. However, a mere systemic effect or a mere local effect does not remove the problem.

Such a harmful content of acetaldehyde mainly in the human mouth, oesophagus, stomach or small intestine or large intestine, and to a small extent in the other areas of the body, can be formed in connection with consuming alcoholic drinks, particularly strong alcoholic drinks, or foodstuffs containing alcohol, or as a consequence of smoking, or when consuming products containing acetaldehyde, in particular in people having atrophic gastritis or an achlorhydric stomach.

"Alcoholic drinks" are ethanol-containing drinks, their ethanol content varying within 0.7% by volume and 84% by volume."

"Alcoholic foodstuffs" refer to foodstuffs containing at least 0.7% of ethanol. Such foodstuffs can be, for example, fermented juices or preserves, or foodstuffs preserved with small amounts of alcohol, pastries, jellies, and mousse seasoned with liqueur or corresponding products containing alcohol.

“Acetaldehyde comprising foodstuffs” refers to foodstuffs containing acetaldehyde. Acetaldehyde is contained in foodstuffs, wherein ethanol has been generated in connection with fermentation, such as beer, cider, wine, home-brewed beer, and other alcoholic drinks, as well as many juices. In certain foodstuffs, such as some milk products, acetaldehyde is used for preservation purposes and to add flavour, or the acetaldehyde is formed in the product as a consequence of microbial activity. For example, sugary juices or sugar-containing foodstuffs in general, provide a food substrate for such microbes. High concentrations of acetaldehyde are formed, for example, in fermented milk products, such as yoghurt. The microbes used to make yoghurt produce acetaldehyde in the yoghurt. As for alcoholic drinks, sherry and Calvados contain especially large amounts of acetaldehyde.

The use of the compositions according to the invention can be of benefit even in connection with consuming light alcoholic drinks or foodstuffs, these drinks or foodstuff containing only small amounts of alcohol.

"In connection with consuming alcoholic drinks" herein refers to the period of time that begins when the subject starts to consume alcoholic drinks and ends when there is no more alcohol in the blood of the subject. However, this term, as such, is not intended to restrict the invention to a reaction of the alcohol in the blood.

Since the compositions of the invention can be beneficial also "in connection with consuming drinks", where the drinks contain materials capable of forming alcohol or acetaldehyde in the body of the subject, or containing only small amounts of alcohol (thus not forming a measurable alcohol content in the blood), the time period can optionally be interpreted to begin 10 to 0 minutes before the subject drinking and ending about 10 minutes after drinking.

Similarly, "in connection with eating" herein refers to the period of time starting 10 minutes before the subject eating and ending 10 minutes after eating.

The composition can, for example, be mixed with the foodstuff or it can be administered before or after eating.

"Smoking", as such, would refer to the use of a tobacco product by inhalation, such as the smoking of a cigarette, cigar or pipe. However, tobacco can be used, for example, by smoking, chewing, wetting or snuffing, and a "tobacco product" refers to any tobacco product, such as a cigarette, cigar, pipe, snuff or chewing tobacco. Thus,"in connection with smoking" herein refers to any use of a tobacco product during a period of time that begins from starting to use tobacco and ends, when said use is stopped.

However, according to our research, smoking, in particular, seems to cause the formation of acetaldehyde in the mouth.

Compositions of the invention

The composition of the present invention contains, as active agents, one or more agents from the group of L-cysteine, D-cysteine and N-acetyl cysteine, as a combination with one or more agents selected from cystine, glutathione and methionine, in any of the forms previously described, the composition optionally including further active agents.

According to an embodiment of the invention, the composition further contains diamine oxidase (i.e. histaminase) as an active agent for degrading excess histamine.

According to another embodiment, a taurine compound or a common water-soluble vitamin is included in the composition.

The composition further comprises one or more pharmaceutical additives, preferably including one or more non-toxic carriers that provide controlled release of said compounds in the desired area(s) of the body.

Controlled release here means the local release of the cysteine compound during at least 5 minutes in the conditions of the mouth, preferably 5 to 15 minutes, or at least 30 minutes in the conditions of the stomach, preferably 0.5 to 8 hours, while the cystine or the glutathione or the methionine is conducted directly to the small intestine for release into the blood stream.

According to the invention, the products obtained from the binding of acetaldehyde to the active agents are safe and non-toxic for the organism.

In addition to cysteines and their derivatives, as well as the cystine, the glutathione and the methionine, the scope of the invention also includes the salts of these compounds, specifically pharmaceutically acceptable salts, in particular water-soluble salts.

It is of advantage to further add to the compositions of the present invention at least one of the substances selected from the group comprising chromium, vitamin B12, A-, D-, E, -C-vitamins, niacin, biotin, thiamine, B2-, B5-, B6-vitamins and folic acid and trace elements, such as chromium, manganese, selenium, zinc and iron, and anti-microbials that decrease

acetaldehyde formation, as these further improve the desired effect. As stated above, the vitamins C, B2 and B5 are particularly useful, especially vitamin C.

Another useful compound to be added to the composition of the invention, which can amplify the acetaldehyde-binding effect of the composition, is also lecithin.

However, only those compounds (and in those amounts), which are non-toxic and suitable for human consumption, are applied to the compositions according to the present invention.

A unit dose of the composition according to the invention can be in the form of, for example, a powder, a tablet, a capsule, a lozenge or a chewing gum. The possibly used tablet can be in a form of a monolithic or multiparticular preparation, while the possibly used capsule can contain the active agents and the additives in, e.g. powder or granule form. Most suitably, the compositions of the invention are formulated into capsules containing the active agents as well as one or more suitable additives, most suitably in granulated form.

The granules, tablets and capsules can be covered by a water-soluble film, which effectively covers or masks the taste of the active agents.

The compositions intended for release in foodstuff or drinks, prior to consumption, can be formulated into for example, powders, which are easily mixed into the foodstuff or drink.

In the case of such a powder, the content of the active agents in the composition can vary between 0.2 to 2 w-% of cysteine and 0.2 to 2 w-% of cystine or glutathione or a combination thereof. The additives typically include agents that mask the taste of the active agents, such as sweeteners or flavourings.

The compositions intended for release in the mouth can be formulated into for example tablets or other preparations, which can be placed between the cheek or the lip and the gum, or preparations that are sucked or chewed in the mouth.

According to the simplest alternative, the unit doses for release in the mouth can be prepared by simply mixing the solid substances, optionally moistured by ethanol, and formulating them into a suitable form, e.g. by pressing into tablets.

The compositions intended for release in the stomach can be formulated into for example tablets or capsules to be swallowed.

In case of a chewing gum, the content of the active agents in the composition can vary between 0.2 to 2 w-% of cysteine and 0.2 to 2 w-% of cystine, glutathione or methionine, or a combination thereof.

In this case, the composition also includes a gum base, in a content of 90 to 99 w-% of the composition, preferably in an amount of 500 to 1500 mg per unit dose.

In case of a lozenge or a tablet to be kept in the mouth, the content of active agents in the composition can vary between 0.3 to 20 w-% of cysteine and 0.3 to 20 w-% of cystine, glutathione or methionine, or a combination thereof.

In this case, the composition also includes one or more diluting agent or filler, in a content of 85 to 98 w-% of the composition, preferably in an amount of 50 to 750 mg per unit dose.

In case of a tablet or capsule to be swallowed, the content of active agents in the composition can vary between 0.5 to 20 w-% of cysteine and 0.5 to 20 w-% of cystine, glutathione or methionine, or a combination thereof.

In these cases, the composition also includes one or more bulking agents, in a content of 85 to 98 w-% of the composition, preferably in an amount of 50 to 750 mg per unit dose.

All types of formulations preferably include an amount of cysteine that is 2 to 50 mg per unit dose, and an amount of cystine, glutathione or methionine, or a combination thereof, that is 2 to 50 mg per unit dose.

According to a preferred embodiment, the composition contains a total amount of active agents, particularly of cysteine compound and additional active agent, which is 2 to 100 mg per unit dose, preferably 2 to 50 mg per unit dose, more preferably 4 to 20 mg per unit dose, and most suitably 5 to 10 mg per unit dose.

Only small amounts/doses are required due to the local area of action of the cysteine, whereby the cysteine is not diluted in any significant extent, and due to the synergistic effect of the active agents, with both the cysteine and the cystine or the glutathione or the methionine relieving the headaches of the subject and thus providing a reduced incidence of headaches via several routes simultaneously. This provides a surprisingly strong effect.

The release of the active compounds in the conditions of the mouth usually takes place in amounts of 15 to 25 mg per hour. In the stomach, the rate of release is generally 40 to 80 mg per hour.

1 or 2 preparations according to the invention can be administered at a time and the administration can be repeated at 2 to 10-hour intervals, most preferably at 4 to 8-hour intervals. In case of chewing gums, a longer interval of 6 to 10 hours can be used, since one gum, after chewing, can be tucked in between the cheek and gums, and chewed again later to release more active agents.

The composition can be formulated to release its active agents in a controlled manner in the mouth or in the stomach.

According to one preferred embodiment of the invention the composition is to release the active agents in the mouth, and comprises, for the purpose of controlling the release, a carrier, usually in the form of a polymer, that does not dissolve or dissolves only poorly in the mouth (hereafter called “a carrier/polymer that does not dissolve in the mouth”).

The polymer not dissolving in the mouth can be any pharmaceutically acceptable additive, such as metacrylate polymer, for example Eudragit RS or S, or ethyl cellulose (EC).

The carrier can also be selected from those forming a gel that adheres to the mucous membranes in the mouth. Such carriers are generally selected from pharmaceutically acceptable polymers. More specifically, the carrier can be selected from the group comprising various chitosans, alginates, such as sodium alginate, aluminium hydroxide, sodium hydrogen carbonate, sodium carboxymethyl cellulose, and sodium hydrogen carbonate.

In addition to the active agents and optional carrier(s), the composition can comprise, for example:

1. Pharmaceutically acceptable diluents (fillers, extenders),
2. Sweeteners, such as sugars and sugar alcohols,
3. Flavourings, and
4. Slip additives/lubricants.

The sugars can comprise, for example, saccharose, fructose or glucose or mixtures thereof. The sugar alcohols can comprise mannitol, sorbitol, maltitol, lactitol, isomalt, or xylitol or mixtures thereof. Preferably, none of the used additives react with the other ingredients in the composition. Not being too sweet, a preferable sweetener comprises mannitol, and its amount in the composition can be quite large; accordingly, it simultaneously functions as a diluent.

The flavourings can comprise, for example, spearmint, peppermint, menthol, citrus fruit, eucalyptus or aniseed or a mixture thereof.

The composition can also comprise other ingredients, such as substances that prevent bad oral smell, substances that function as breath fresheners and/or prevent dental caries, or the preparation can comprise vitamins. The composition can also comprise substances that increase salivation.

Further, the composition can comprise, as a further additive, a bulking agent, preferably an inert agent, particularly in a content of 20-70 w-%, preferably 40 to 60 w-%, most preferably about 50 w-%.

The inert bulking agent can be for example dicalcium hydrogen phosphate, microcrystalline cellulose (MCC), or another corresponding non-swelling agent.

According to a preferred embodiment of the present invention, a typical preparation/unit dose (such as one tablet) for release in the mouth can comprise or consist of the following:

Cysteine	2 to 10 mg
Cystine/glutathione/methionine	2 to 10 mg
Diluting agent(s)/sweetener(s)	50 to 750 mg
Flavouring(s)	q.s.
Lubricant(s) (0.5 to 3% by weight)	5 to 25 mg

The tablets can be prepared by mixing a powdery mass and compressing it into sucking tablets by any well-known methods.

If the amount of cysteine or cystine or glutathione or methionine is increased, the amount of diluent(s)/sweetener(s) and flavourings can also be increased, as the taste of the cysteine preferably is disguised.

A typical preparation/unit dose can be formulated into a chewing gum, and essentially comprises or consists of the following:

Cysteine	2 to 10 mg
Cystine/glutathione/methionine	2 to 10 mg
Gum base (comprising e.g. sweeteners)	500 to 1500 mg
Flavouring	q.s.
Lubricant (0.5 to 3% by weight)	5 to 30 mg

The gum base can be formed from medicated chewing gum (Morjaria, Y. et al., Drug Delivery Systems & Sciences, vol. 4, No. 1, 2004) or natural or synthetic elastomers, softeners, waxes or lipids. Natural gum bases, including crude rubber and smoked natural rubber, are permitted by the FDA. However, modern gum bases are mostly synthetic and include styrene-butadiene rubber, polyethylene and polyvinyl acetate.

The gum base generally constitutes 15 to 40 w-% of a chewing gum. The remaining portion includes mainly medicating agents, sugars, sweeteners, softeners, flavourings and colouring agents.

The majority of the chewing gum-based drug delivery systems are prepared using conventional methods. However, directly compressible powder gums are modern alternatives to the medicated chewing gums. Pharmagum is a compressible new gum system. It is a mixture of polyol(s) and/or sugars with a gum base. A formulation that contains Pharmagum gums can be compressed into a gum tablet by using conventional tablet presses. The manufacturing method is quick and inexpensive. The amount of gum base in the preparation, comprising sweeteners, can be 50 to 500 mg, preferably 500 to 1500 mg.

Pharmagum S contains rubber base and sorbitol, Pharmagum M contains rubber base, mannitol, and isomalt.

The composition can be prepared by mixing a powdered mass and compressing it into chewable pieces.

The preparation can be a buccal tablet comprising:

Cysteine	2 to 10 mg
Cystine/glutathione/methionine	2 to 10 mg
Non-ionized macro molecules	5 to 25 mg
Ionizing macro molecules	2 to 10 mg
Flavouring(s)	q.s.
Lubricants	0.5 to 3% by weight

The non-ionized macro molecules include, e.g., methylcellulose (MC), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG). The ionizing polymers include, e.g., sodium carboxymethyl cellulose (NaCMC), alginic acid, sodium alginate, chitosan, polycarbofile (Noveon^{TM}) and carbomer (Capropol^{TM}).

The non-ionized macro molecules generally constitute 40 to 80 w-% of a buccal tablet, whereas the ionizing polymers generally constitute 20 to 60 w-% of such a tablet.

The preparation can also be a sublingual tablet essentially comprising or consisting of the following:

Cysteine	2 to 10 mg
Cystine/glutathione/methionine	2 to 10 mg
Diluent(s)/sweetener(s) q.s.	50 to 500 mg
Flavouring(s)	q.s.
Lubricants	0.5 to 3% by weight

The diluents include, e.g., lactose, calcium phosphates, starch, carboxymethyl cellulose, hydroxymethyl cellulose. The sweetener can be, for example, mannitol or xylitol.

The diluents generally constitute 90 to 98 w-% of a sublingual tablet.

According to another preferred embodiment of the invention, the composition is formulated to release the active agents in the stomach, and comprises, for the purpose of controlling the release, a carrier, such as a polymer, that does not dissolve or dissolves only poorly in the stomach (here called simply "a carrier/polymer that does not dissolve in the stomach"). The composition is, for this purpose, preferably formulated by pressing it into tablets or by enclosing the composition into capsules. Alternatively the composition can be covered by a water insoluble film.

A carrier not dissolving in the stomach can be a polymer, such as metacrylate polymer, for example Eudragit RS or S, or ethyl cellulose.

Such polymers are preferably present in a content of 10-50 w-%, more preferably 20 to 40 w-%, most suitably 20 to 30 w-% of the entire composition.

The carrier can also form a gel in the stomach that floats in the contents of the stomach, or the composition can be formulated into a liquid preparation taken orally (mixture), the physical structure of which preferably is a gel. Alternatively, the carrier of the composition

can attach to the mucous membrane of the stomach, thus causing the entire preparation, including active agent, to attach to the mucous membrane.

The composition can also comprise a bulking agent, preferably an inert agent, such as dicalcium hydrogen phosphate, microcrystalline cellulose (MCC), or another corresponding non-swelling agent, for example in a content of 20-70 w-%, preferably 40 to 60 w-%, most preferably about 50 w-%, of the entire composition.

According to one preferred embodiment of the invention the composition comprises matrix granules not dissolving in stomach. Such a composition can comprise for example:

Cysteine	5 to 40 w-% (preferably 25 w-%)
Cystine/glutathione/methionine	5 to 40 w-% (preferably 25 w-%)
Polymer not dissolving in stomach	10 to 50 w-% (preferably 20 to 30 w-%)
Inert bulking agent	20 to 70 w-% (preferably 40 to 60 w-%)
Ethanol	q.s.

The polymer not dissolving in stomach can in the above composition be any commonly used additive, such as metacrylate polymer, for example Eudragit RS or S, or ethyl cellulose (EC). The inert bulking agent may be for example dicalcium hydrogen phosphate, microcrystalline cellulose (MCC), or other corresponding non-swelling agent. The solid substances are mixed and moistured by ethanol. The moisture mixture is granulated by using in pharmaceutical industry well known methods and devices. The dried granules can be used as such or distributed into dosages, for example into capsules.

According to another preferred embodiment of the invention the composition comprises matrix tablets not dissolving in stomach. Such a composition can comprise for example:

Cysteine	5 to 40 w-% (preferably 25 w-%)
Cystine/glutathione/methionine	5 to 40 w-% (preferably 25 w-%)
Polymer not dissolving in stomach	10 to 50 w-% (preferably 20 to 30 w-%)
Inert bulking agent	20 to 70 w-% (preferably 20 to 50 w-%)

The polymer not dissolving in stomach may in the above composition be any in pharmaceutical industry commonly used additive, such as metacrylate polymer, for example Eudragit RS or S, or ethyl cellulose (EC). The inert bulking agent can be, for

example, dicalcium hydrogen phosphate, microcrystalline cellulose (MCC), or another corresponding non-swelling agent. The solid substances are mixed and the mixture is granulated by using, for example, ethanol or a hydrophilic polymer solution. The granules are pressed into tablets using methods and devices well known in the pharmaceutical industry. The release of the active compound(s) is here based on the diffusion of the water-soluble effective compound(s) from the pores formed to the tablet matrix.

According to another preferred embodiment of the invention the composition comprises one or more porous film forming agents for coating the preparation, such as ethyl cellulose or hydroxypropyl methylcellulose, or a combination thereof. Most suitably a combination of ethyl cellulose and hydroxypropyl methylcellulose is used, such as a combination with a relative amount of EC to HPMC being 3/2 to 7/3.

Such a composition covered by a porous film can comprise, for example:

Cysteine	1 to 50 w-% (preferably 20 to 50 w-%)
Cystine/glutathione/methionine	1 to 50 w-% (preferably 20 to 50 w-%)
Water-soluble bulking agent(s)	50 to 80 w-% (preferably 30 to 60 w-%)
Porous film forming agent(s)	q.s.

The water-soluble bulking agent can, in such a composition, be for example lactose or some other water-soluble bulking agent commonly used in the pharmaceutical industry. The solid substances are mixed and the mixture is pressed into tablets using methods and devices well-known in the pharmaceutical industry. The porous film can be prepared from a water-soluble polymer, such as hydroxypropyl methyl cellulose (HPMC), or a water-insoluble polymer, such as ethyl cellulose (EC), preferably from a mixture of such polymers. The relative amount of the film forming substances, for example EC and HPMC, is preferably 2-5 parts water-insoluble polymer and 1-2 parts water-soluble polymer. In the conditions of the stomach the water-soluble polymer dissolves and pores are formed in the remaining water insoluble polymer. The release of the effective compound(s) is here based on the diffusion of the water-soluble effective compound(s) from the pores formed in the film. The film forming substances effectively mask also the taste of the active agent(s).

Treatment

The composition comprising effective amounts of cysteine and cystine or glutathione or methionine is administered into the foodstuff or drink soon to be consumed by a subject, or directly to the subject, in a suitable amount, which can contain, for example, 0.2 to 20 w-% of cysteine and 0.02 to 20 w-% of cystine or glutathione or methionine or a combination thereof, most suitably directly to the subject in connection with the subject consuming alcohol-containing drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff, or in connection with the subject smoking.

Furthermore, it is preferred that the preparation has a shape that makes it easy to keep in the mouth or to swallow. However, it is of advantage if the composition for release of active agents in the stomach is in the form of a preparation having a diameter of at least 7 mm, preferably 8 to 15 mm, more preferably 11 to 15 mm. This assists the preparation to stay in the stomach sufficient time for the controlled release of the active agents.

Thus, the present invention provides preparations and methods, which can be used to reduce the incidence of severe headaches, particularly cluster headaches and migraines.

For example, the incidence of severe headaches can be reduced using a method of treatment that comprises the following stages:

a) a human subject at least occasionally suffering from severe headaches is provided with a composition containing cysteine and cystine or glutathione or methionine, to be administered in connection with consuming alcoholic drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff, or in connection with smoking,
b) the subject self-administers the composition, and
c) the subject is allowed to eat, drink or smoke,

whereby the cysteine and the cystine or the glutathione or the methionine bind the acetaldehyde generated or carried to the body in connection with consuming the drink or the foodstuff, and

d) optionally, the stages a) to c) are repeated as many times as feels necessary.

Other applications of the invention

According to an embodiment of the invention the composition of the present invention is administered to human subjects having atrophic gastritis, in addition to suffering from said severe headaches.

Atrophic gastritis, among others, enhances the risk of malabsorption of vitamin B12, and may lead to pernicious anemia. Malabsorption of micronutrients may lead to serious secondary diseases of the central nervous system and to osteoporosis. Half of the people with atrophic gastritis of corpus of the stomach can have an exceptionally low vitamin B12 level and at least half of these simultaneously have increased serum levels of homocysteine. Thus, the composition of the present invention, supplemented with vitamin B12, is particularly suitable for use by such people. The vitamin B12 will be released with the other active agents and carried with at least a portion of the cystine or the glutathione or the combination thereof to the blood stream for a systemic effect.

Vitamin B12 deficiency is a strong risk factor for neurodegenerative disorders, such as dementia, depression and polyneuropathies. The deficiency of vitamin B12 is one common reason for hyperhomocysteinemia, an independent risk factor for atherosclerosis, strokes and heart attacks. Because of corpus atrophy and poor diet even 15% of individuals over the age 50 are suffering from a preventable epidemic of vitamin B12 deficiency.

With the early detection of corpus atrophy by routine screening for suitable biomarkers, for example by GastroPanel® screening, and subsequent treatment, possible neurological disabilities (e.g. dementia, depression and polyneuropathies) and vascular diseases (e.g. stokes and heart attacks) can be prevented. The ageing of the population is increasing the need for screening for said biomarkers, for example by the GastroPanel® examination and screening, and, in other words, for diagnosis of atrophic gastritis and related risks and diseases.

To the compositions of the present invention, in addition to vitamin B12, also other vitamins can be added, such as vitamins A, D, E and C, niacin, biotin, thiamine, B2, B5, B6 and folic acid as well as trace elements, such as chromium, manganese, selenium, zink

and iron. Ferrous compounds are of particular advantage, since atrophic gastritis is often connected with iron deficiency anemia.

According to an embodiment of the invention, the above-described treatment is preceded by a diagnosis as to a possible *H. pylori* infection, preferably using a test that reliably provides a diagnosis also as to atrophic gastritis. Thus, the magnitude of the problems caused by acetaldehyde in the gastrointestinal tract (GI tract) can be estimated.

It is clear from the literature that the biomarkers pepsinogens I and II (PG-I and PG-II) as well as gastrin-17 (G-17) measure atrophic gastritis accurately, possibly on the average even more accurately than gastroscopy. The PG I/PG II ratio also correlates with the occurrence of precancerous and cancerous changes in the oesophagus. These biomarkers are secreted into the stomach lumen, and small quantities are transferred to the circulation where they reflect the concentrations in the stomach.

The level of PGI and the ratio PGI/PGII are markers of the function and structure of the corpus mucosa, and the level of G-17, which is usually measured in a fasting blood sample, is a marker of the function and structure of the antrum mucosa. Including for example *H. pylori* antibodies, such as *H. pylori* IgG and IgA, as biomarkers in the test will provide information also as to a possible *H. pylori* infection. Thus, said biomarkers (PG-I, PG-II and their ratio in combination with G-17 and H. pylori IgG and IgA) complement each other so as to form a diagnostic panel.

The levels of these biomarkers are preferably measured using an ELISA assay on a blood, plasma or serum sample of a patient, particularly on a fasting plasma sample. If a patient with an *H. pylori* infection and low levels of G-17 does not want to have invasive gastroscopy, atrophic gastritis of the antrum can be confirmed or excluded by assaying the concentration of protein-stimulated G-17 in plasma in addition to said examination from a fasting plasma sample. An examination procedure particularly suitable for said purpose is the GastroPanel® examination.

The role of PG-I as a marker of atrophic gastritis is well known. Lately also evidence regarding its usefulness in determining the condition of particularly the corpus mucosa has been provided.

The PGI/PGII ratio has lately been shown to decrease linearly with increasing grade of atrophic gastritis in the corpus. The ratio is < 3.0 when atrophic gastritis is advanced (moderate or severe) in the gastric corpus. It has been shown that the risk of gastric cancer is increased (5-fold) when the PGI/PGII ratio is low.

The role of measuring the amidated peptide hormone gastrin-17 is less studied than the pepsinogens, but yet already of considerable clinical interest. In the stomach, gastrin-17 has the task of stimulating the secretion of hydrochloric acid. Likewise, there is a negative feed-back control such that hydrochloric acid inhibits the formation of G-17.

Combining the G-17 determination with those of PG I and II helps to distinguish the cases where the atrophic gastritis (AG) is limited to the gastric *fundus* and *corpus* regions (PG-I is low, but G-17 is high), from those where also the *antrum* is affected (both PG-I and G-17 are low). Such a distinction is clinically important, because the latter (*panatrophy)* carries the highest known risk for gastric cancer.

To sharpen the examination further, a fasting G-17 assay may be compared with a determination after stimulation by a protein meal. If a low G-17 level is not clearly raised by such stimulation, it provides good evidence for atrophy in the *antrum* domain. However, if an initially low G-17 level is clearly raised by such stimulation, the gastric *antrum* is likely to be physiologically functional, and a low resting G-17 level (e.g., below 2 pmol/L) is in such cases a strong indication of abnormally high acidity in the stomach, in which case the risk of Barrett´s oesophagus is elevated. Conversely, a pathologically high level of fasting G-17 is strongly indicative of hypo- or achlorhydria, which may be caused by AG limited to the *corpus* region, or indeed by PPI treatment.

The following examples are included merely for illustrative purposes, and are not intended to limit the invention.

Examples

Example 1 – Preparation of sucking tablets

Sucking tablets were prepared, one type comprising:

L-Cysteine	20 mg
Cystine	20 mg
Mannitol (or an equivalent sugar or sugar alcohol)	750 mg
Flavouring	q.s.
Magnesium stearate	10 mg

The further compositions varied in cysteine content, which was 1.25 mg, 2.5 mg, 5 mg, and 10 mg of cysteine.

The compositions were prepared by mixing a powdery mass and compressing it into sucking tablets.

Example 2 – Preparation of chewing gums

A chewing gum was prepared, comprising:

Cysteine	20 mg
Cystine	20 mg
Pharmagum S, M or C	1000 mg
Flavouring	q.s.
Magnesium stearate	20 mg

The composition was prepared by mixing a powdery mass and compressing it into chewing gums.

Another composition was prepared, comprising 500 mg of Pharmagum S or M, and 20 mg of magnesium stearate.

Example 3 – Preparation of buccal tablets

A buccal tablet was prepared, comprising:

Cysteine	20 mg
Cystine	20 mg
Methocel	25 mg
Carbopol	7 mg
Flavouring	q.s.
Magnesium stearate	2 mg

The composition was prepared by mixing a powdery mass and compressing it into buccal tablets.

Example 4 – Preparation of sublingual tablets

A sublingual tablet was prepared, comprising:

Cysteine	10 mg
Cystine	10 mg
Mannitol	250 mg
Flavouring	q.s.
Magnesium stearate	5 mg

The composition was prepared by mixing a powdery mass and compressing it into sublingual tablets.

Example 5 – Effect of the composition on acetaldehyde levels

Five smokers (of the age of 29 ± 2.8) participated in a study, in which three cigarettes were smoked (with cleaning periods in between). While smoking each cigarette (in 5 minutes time), the voluntaries sucked tablets blindfold, containing a placebo, 1.25 mg, 2.5 mg, 5 mg, 10 mg or 20 mg of L-cysteine. The acetaldehyde in the saliva samples was analysed by gas chromatography after 0, 5, 10, 20 minutes from starting to smoke.

The L-cysteine tablets (5 mg, 10 and 20 mg) removed from the saliva all of the acetaldehyde originating from tobacco (see Fig. 1). The average salivary acetaldehyde contents immediately after smoking were 191.2 ± 48.5 μM, 0 μM, 0 μM, 0 μM with the placebo and the 5 mg, 10 mg, and 20 mg L-cysteine tablets, respectively.

The study showed that even 5 mg of L-cysteine, when delivered with a melting tablet, completely inactivated the carcinogenic acetaldehyde in the saliva during smoking. The L-cysteine tablet of 1.25 mg reduced the amount of acetaldehyde by about two thirds compared with the placebo.

Example 6 – Increase in salivary acetaldehyde levels following smoking and drinking

Tobacco smoke contains acetaldehyde, which during smoking becomes dissolved in saliva (see Fig. 2). In this study, both smokers and non-smokers at first took a small dose of alcohol and thereafter the smokers smoked 6 cigarettes for about 5 minutes each. During smoking, salivary acetaldehyde exceeds remarkably the carcinogenic level.

Via swallowing, the salivary acetaldehyde derived either from alcohol or smoking is distributed from the oral cavity to the pharynx, the oesophagus and the stomach. Thus, the carcinogenic effect is not limited to the mouth.

The strongest evidence for the local carcinogenic action of acetaldehyde provides studies with ALDH2-deficient Asians, who form an exceptional human "knock-out model" for long-term acetaldehyde exposure.

In the subjects with ALDH2-deficiency (Flushers) the additional salivary acetaldehyde appeared to be derived from salivary glands.

In several epidemiological studies from Asian countries it has been uniformly shown that ALDH2-deficiency associates with over 10-fold risk of upper digestive tract cancers. The association is strongest among heavy drinkers but in addition significant also among normal alcohol consumers. Thus, smokers are clearly also at high risk.

In conclusion, acetaldehyde derived from tobacco appears to act in the upper digestive tract as a local carcinogen in a dose-dependent and synergistic way.

Example 7 – Acetaldehyde-elimination using cysteine

Cysteine is a sulfur-containing amino acid. Its average intake is about 1g/day. Cysteine condensates with and thereby deactivates the reactive and carcinogenic acetaldehyde by forming 2-methyl—thiazolidine-4-carboxylic acid (MTCA).

For example a lozenge containing as little as 5mg of L- or D-cysteine totally eliminates acetaldehyde from saliva during smoking (Fig. 3).

Harmful effects of reactive acetaldehyde may be prevented by binding it to the cysteine. This semi-essential amino acid inactivates acetaldehyde by a non-enzymatic binding, forming a more stable compound, 2-methylthiazolidine-4-carboxylic acid. For example, a tablet and chewing gum containing L-cysteine has been developed in order to eliminate acetaldehyde exposure during smoking (Fig. 4).

Claims

1. A non-toxic solid pharmaceutical composition for oral administration, for reducing the incidence of, or preventing, severe headaches, the composition containing one or more cysteine compound from the group of L-cysteine, D-cysteine and N-acetyl cysteine as active agents, **characterized** in that the cysteine compound is combined with one or more additional active agents, at least one of which being selected from the group of cystine, glutathione and methionine, the composition further containing one or more pharmaceutical additives, including one or more non-toxic carriers that provide controlled release of the active agents either into the saliva during at least 5 minutes in the conditions of the mouth or into the stomach during at least 15 minutes in the conditions of the stomach.

2. The composition of Claim 1 for reducing the incidence of, or preventing, migraine or cluster headaches, particularly cluster headaches.

3. The composition of Claim 1 or 2, **characterized** in that it is in the form of a powder, tablet, lozenge, capsule or chewing gum.

4. The composition of any preceding claim, **characterized** in that the active agents are selected from L-cysteine and one or more of cystine, glutathione and methionine, preferably from L-cysteine and one of the latter, the latter most suitably being glutathione.

5. The composition of any preceding claim, **characterized** in that the active agents are selected from one or more cysteine compounds and glutathione, preferably from one cysteine compound and glutathione, the former most suitably being L-cysteine.

6. The composition of any preceding claim, **characterized** in that it further contains diamine oxidase as an active agent for degrading excess histamine.

7. The composition of any of claims 1 to 5, **characterized** in that the active agents consist of amino acids selected from L-cysteine, D-cysteine, N-acetyl cysteine, cystine, glutathione and methionine.

8. The composition of any preceding claim, **characterized** in that it further contains a vitamin or a similar nutritious supplement selected from a taurine compound or a common water-soluble vitamin, such as vitamin C, B_2 or B_5, or a salt thereof, preferably selected from vitamin C or a salt of taurine, such as a magnesium or calcium salt, more preferably selected from magnesium taurinates, the supplement most suitably being magnesium N-acetyl taurinate.

9. The composition of any preceding claims, **characterized** in that it contains a total amount of active agents, particularly of cysteine compound and additional active agent, which is 2 to 50 mg per unit dose, preferably 2 to 20 mg per unit dose, and most suitably 4 to 10 mg per unit dose.

10. The composition of any preceding claim, **characterized** in that it is formulated for controlled release of the active agents in the mouth or the stomach, or for release into a food product or drink prior to consumption.

11. The composition of Claim 10, **characterized** in that the amount of cysteine compound in a formulation for release of the active agents in the mouth is 2 to 10 mg per unit dose, preferably about 5 mg, whereas the amount of cystine or glutathione or methionine or a combination thereof in such a formulation is 2 to 10 mg per unit dose, preferably about 5 mg, and the amount of cysteine in a formulation for release of the active agents in the stomach is 10 to 50 mg per unit dose, preferably about 20 mg, whereas the amount of cystine or glutathione or methionine or a combination thereof in such a formulation is 10 to 50 mg per unit dose, preferably about 20 mg.

12. The composition of any preceding claim, **characterized** in that it comprises, as additives, diluents, such as fillers or extenders, sweeteners, such as sugars or sugar alcohols, flavourings, lubricants, gum base, non-ionized polymers or ionizing polymers, or a combination of two or more of these.

13. The composition of claim 12, **characterized** in that the gum base is selected from natural or synthetic elastomers, softeners, waxes and lipids, the natural gum bases preferably being selected from crude rubber and smoked natural rubber, and the synthetic

gum bases preferably being selected from styrene-butadiene rubber, polyethylene and polyvinyl acetate.

14. The composition of claim 12, **characterized** in that the non-ionized polymers are selected from methylcellulose (MC), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG).

15. The composition of claim 12, **characterized** in that the ionizing polymers are selected from sodium carboxymethyl cellulose (NaCMC), alginic acid, sodium alginate, chitosan, polycarbofile (Noveon^{TM}) and carbomer (Capropol^{TM}).

16. The composition of claim 12, **characterized** in that the diluents are selected from lactose, calcium phosphates, starch, carboxymethyl cellulose, hydroxymethyl cellulose.

17. The composition of any preceding claim, **characterized** in that it has been formulated into chewing gums, wherein the gum base constitutes 15 to 40% of a chewing gum, the remaining portion including agents selected from medicating agents, sugars, sweeteners, softeners, flavourings and colouring agents.

18. The composition of any of claims 1 to 16, **characterized** in that it has been formulated into buccal tablets containing non-ionized macro molecules in a content of 40 to 80 w-% and ionizing polymers in a content of 20 to 60 w-%.

19. The composition of any of claims 1 to 16, **characterized** in that it has been formulated into sublingual tablets containing diluents in a content of 90 to 98 w-%.

20. The composition of any of claims 1 to 16, **characterized** in that it has been formulated into matrix granules or matrix tablets containing polymers not dissolving in the stomach in a content of 10 to 50 w-%, and bulking agent in a content of 20 to 70 w-%.

21. The composition of any preceding claim, **characterized** in that it is dosed by placing 1 or 2 preparations formulated from the composition in the mouth at a time and replacing them with new ones at 4 to 10-hour intervals, most preferably at 6 to 8-hour intervals.

22. A combination of one or more cysteine compounds, selected from L-cysteine, D-cysteine and N-acetyl cysteine, with one or more of the compounds cystine, glutathione and methionine for use as a medicine.

23. A method for reducing the incidence of severe headaches in human subjects, **characterized** by carrying out the following stages:

a) providing a subject that at least occasionally suffers from severe headaches with a composition according to any of claims 1 to 20, to be self-administered in connection with consuming alcoholic drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff, or in connection with smoking,

b) allowing the subject to self-administer said composition, and

c) allowing the subject to eat, drink or smoke,

whereby the cysteine and the cystine or the glutathione or the methionine bind the acetaldehyde generated in or carried to the body in connection with the subject consuming the drink or the foodstuff, and

d) optionally, repeating the stages a) to c) as many times as feels necessary.

24. The method of Claim 23 for reducing the incidence of or preventing migraine or cluster headaches.

25. The method of Claim 23 or 24, **characterized** by administering the composition to the subject in step b) by placing 1 or 2 preparations formulated from the composition in the mouth or swallowing them, and the optional step d) is carried out by replacing the preparations with new ones at 4 to 10-hour intervals, most preferably at 6 to 8-hour intervals, and optionally also repeating step c).

Fig. 1

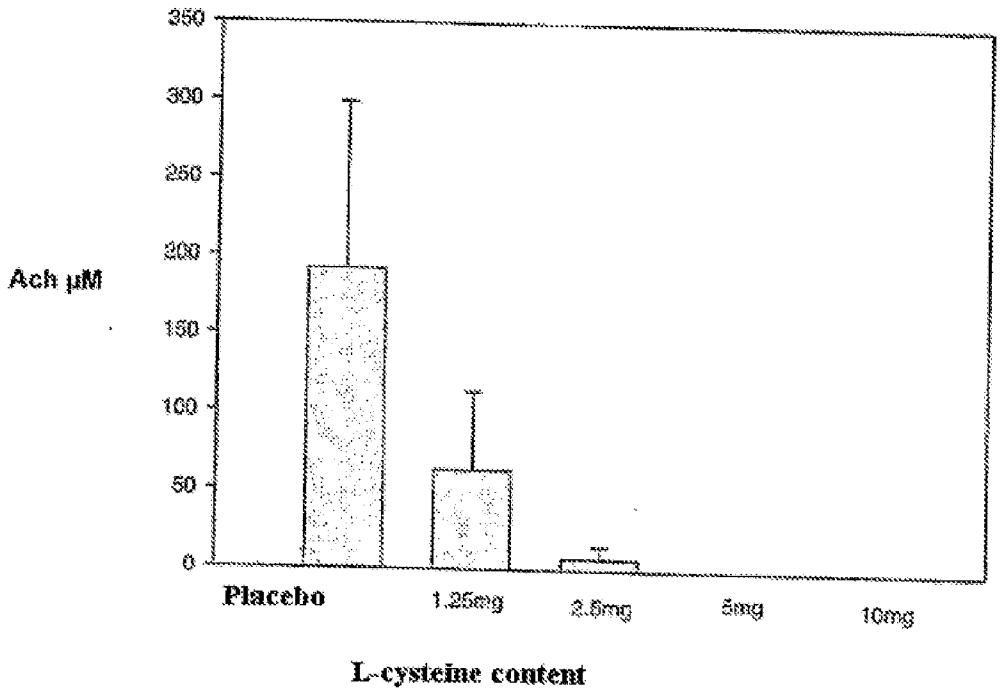

Ach µM
350
300
250
200
150
100
50
0
Placebo
1.25mg
2.5mg
5mg
10mg
L-cysteine content

Fig. 2

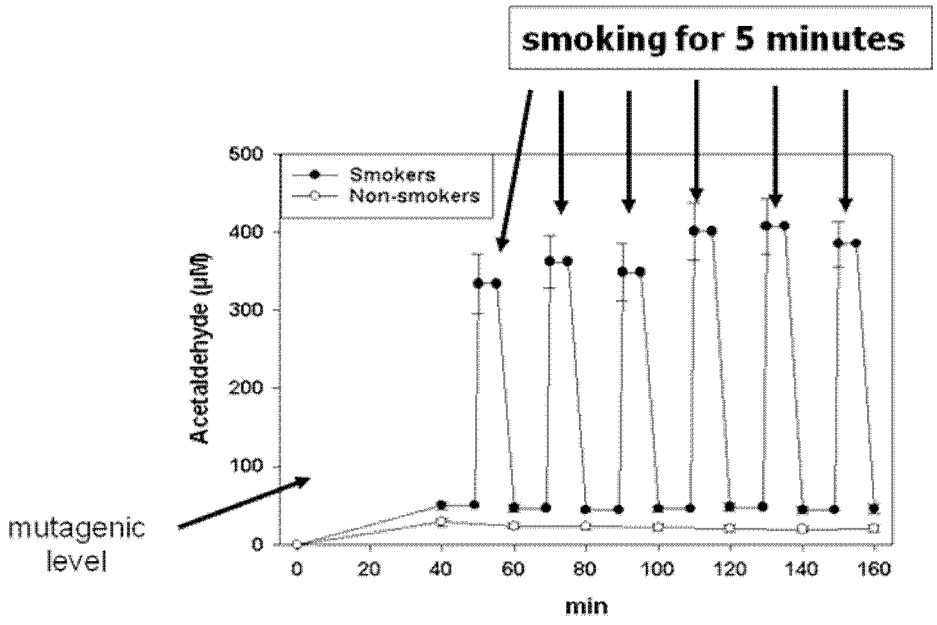

smoking for 5 minutes
Smokers
Non-smokers
Acetaldehyde (µM)
500
400
300
200
100
0
mutagenic level
0
20
40
60
80
100
120
140
160
min

Fig. 3

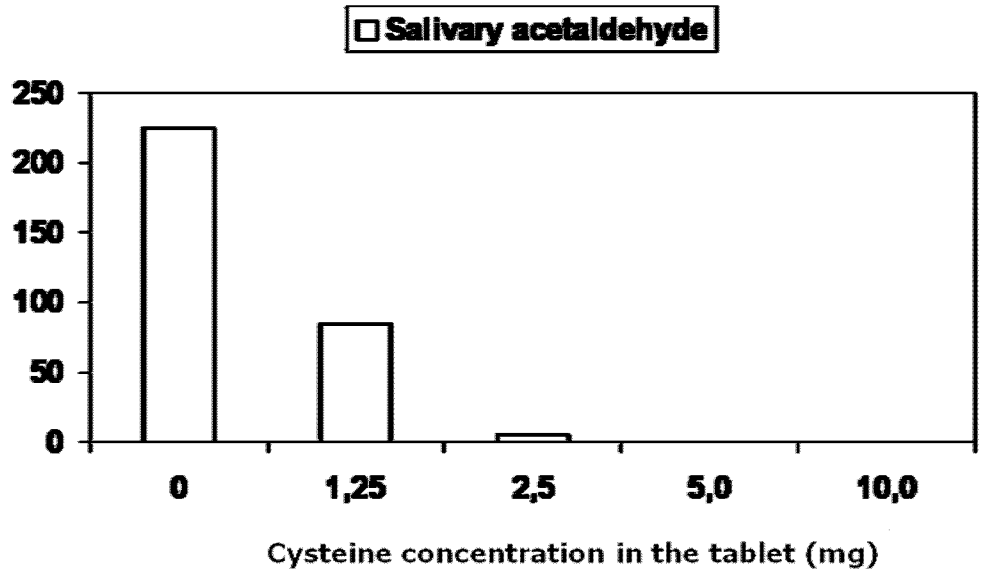
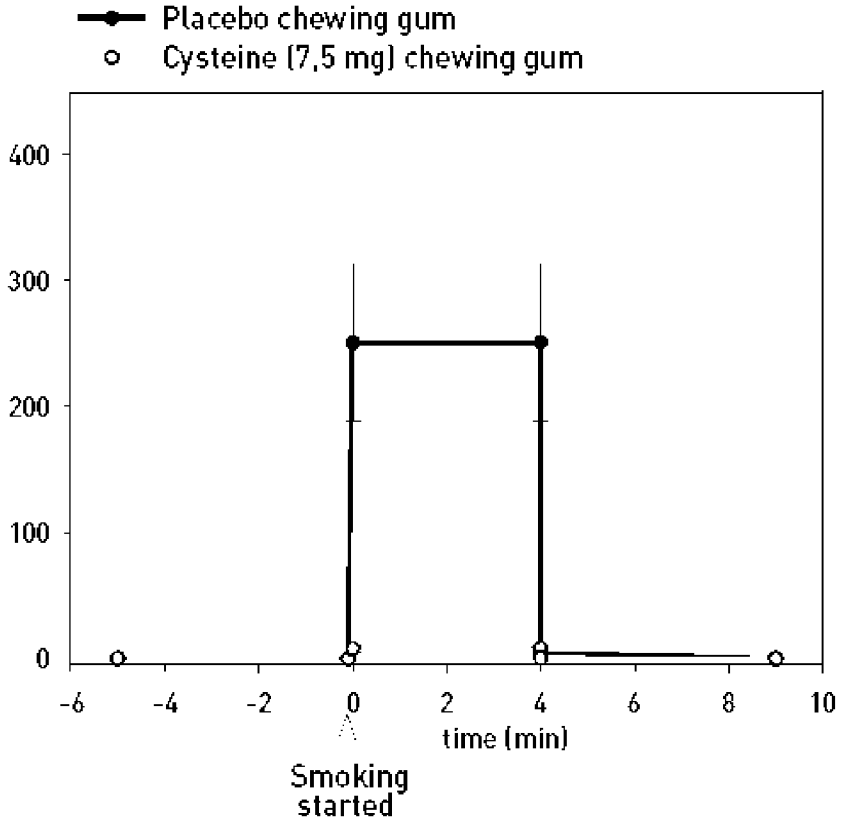

Salivary acetaldehyde
250
200
150
100
50
0
0
1,25
2,5
5,0
10,0
Cysteine concentration in the tablet (mg)

Fig. 4


Placebo chewing gum
Cysteine (7,5 mg) chewing gum
400
300
200
100
0
-6
-4
-2
0
2
4
6
8
10
time (min)
Smoking started

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2013/050582

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P

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

FI, SE, NO, DK

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

EPO-Internal, WPI, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0236098 A1 (LICENTIA LTD [FI]) 10 May 2002 (10.05.2002) cited in the application, claims 1, 2, 7-33	1-21
X	WO 2012027603 A2 (CLARITY PRODUCTS LTD LIABILITY COMPANY [US]) 01 March 2012 (01.03.2012) page 3, lines 9-18, page 7, lines 13-21, claims 1 and 2	22
Y		1-21
A	US 2008075710 A1 (CORNETT ERIK T [US] et al.) 27 March 2008 (27.03.2008) claims 1-4	1-22
A	EP 2374448 A1 (LABTEC GMBH [DE]) 12 October 2011 (12.10.2011) claim 6	1-22

☐ 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2013 (28.08.2013)	05 September 2013 (05.09.2013)

Name and mailing address of the ISA/FI	Authorized officer
National Board of Patents and Registration of Finland P.O. Box 1160, FI-00101 HELSINKI, Finland	Antti Hoikkala
Facsimile No. +358 9 6939 5328	Telephone No. +358 9 6939 500

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2013/050582

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.: 23-25
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 23-25 relate to a method or treatment of the human body by therapy (PCT Rule 39.1 (iv)).

2. ☐ Claims Nos.:
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:

3. ☐ Claims Nos.:
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 additional fees, this Authority did not invite payment of 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/FI2013/050582

Patent document cited in search report	Publication date	Patent family members(s)	Publication date
WO 0236098 A1	10/05/2002	AT 522203 T	15/09/2011
		AU 1239502 A	15/05/2002
		CN 1486177 A	31/03/2004
		CN 100467016 C	11/03/2009
		EA 009335 B1	28/12/2007
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		EP 1339394 B1	31/08/2011
		ES 2370811 T3	23/12/2011
		FI 20002392 A	01/05/2002
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		JP 2008515859 A	15/05/2008
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		WO 2006037848 A1	13/04/2006
WO 2012027603 A2	01/03/2012	None	
US 2008075710 A1	27/03/2008	None	
EP 2374448 A1	12/10/2011	CN 102946856 A	27/02/2013
		MX 2012011445 A	18/03/2013
		WO 2011124570 A2	13/10/2011

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI2013/050582

CLASSIFICATION OF SUBJECT MATTER

Int.Cl.
A61K 31/198 (2006.01)
A61K 38/06 (2006.01)
A61K 9/20 (2006.01)
A61K 9/00 (2006.01)
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A61P 25/06 (2006.01)

(19)中华人民共和国国家知识产权局

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A61K 31/198(2006.01)
A61K 38/06(2006.01)
A61K 9/20(2006.01)
A61K 9/00(2006.01)
A61K 9/68(2006.01)
A61P 25/06(2006.01)

权利要求书2页 说明书16页 附图3页

(54)发明名称

预防头痛的组合物

(57)摘要

本发明涉及一种用于口服给予的非毒性固体药用组合物，其包含一种或多种选自L-半胱氨酸、D-半胱氨酸和N-乙酰基半胱氨酸的半胱氨酸化合物，组合有一种或多种另外的活性剂，所述活性剂的至少一种选自胱氨酸、谷胱甘肽和甲硫氨酸，所述组合物还包含一种或多种药用添加剂。此外，本发明涉及一种减少严重头痛，特别是偏头痛和/或丛集性头痛的发生率的方法。

CN 104427983 A

1. 一种用于口服给予的非毒性固体药用组合物，其用于减少严重头痛的发生率，或预防严重头痛，所述组合物包含一种或多种选自 L- 半胱氨酸、D- 半胱氨酸和 N- 乙酰基半胱氨酸的半胱氨酸化合物作为活性剂，特征在于所述半胱氨酸化合物与一种或多种另外的活性剂组合，所述另外的活性剂的至少一种选自胱氨酸、谷胱甘肽和甲硫氨酸，组合物还包含一种或多种药用添加剂，包括一种或多种非毒性载体，所述载体提供在口腔的环境下至少 5 分钟期间控制释放活性剂进入唾液，或者在胃的环境下至少 15 分钟期间控制释放活性剂进入胃。

2. 权利要求 1 的组合物，其用于减少偏头痛或丛集性头痛、特别是丛集性头痛的发生率，或预防偏头痛或丛集性头痛、特别是丛集性头痛。

3. 权利要求 1 或 2 的组合物，特征在于其以散剂、片剂、锭剂、胶囊或口香糖的形式呈现。

4. 前述权利要求中任一项的组合物，特征在于活性剂选自 L- 半胱氨酸以及以下的一种或多种 ：胱氨酸、谷胱甘肽和甲硫氨酸 ；优选选自 L- 半胱氨酸和所述后者中的一种 ；所述后者最适合是谷胱甘肽。

5. 前述权利要求中任一项的组合物，特征在于活性剂选自一种或多种半胱氨酸化合物和谷胱甘肽，优选选自一种半胱氨酸化合物和谷胱甘肽，所述前者最适合是 L- 半胱氨酸。

6. 前述权利要求中任一项的组合物，特征在于其还含有作为用于降解过量组胺的活性剂的二胺氧化酶。

7. 权利要求 1-5 中任一项的组合物，特征在于活性剂由选自 L- 半胱氨酸、D- 半胱氨酸、N- 乙酰基半胱氨酸、胱氨酸、谷胱甘肽和甲硫氨酸的氨基酸组成。

8. 前述权利要求中任一项的组合物，特征在于其还含有维生素或类似的营养补充剂，所述维生素或类似的营养补充剂选自牛磺酸化合物或普通的水溶性维生素，例如维生素 C、B_2 或 B_5，或其盐，优选地选自维生素 C 或牛磺酸的盐，例如镁或钙盐，更优选地选自牛磺酸镁，补充剂最适合是 N- 乙酰基牛磺酸镁。

9. 前述权利要求中任一项的组合物，特征在于其含有活性剂，特别是半胱氨酸化合物和另外的活性剂，其总量是 2-50 mg 每单位剂量，优选是 2-20 mg 每单位剂量，和最适合是 4-10 mg 每单位剂量。

10. 前述权利要求中任一项的组合物，特征在于其被配制为用于在口腔或胃中控制释放活性剂，或用于在消费前释放进入食物产品或饮料。

11. 权利要求 10 的组合物，特征在于用于在口腔中释放活性剂的制剂中半胱氨酸化合物的量是 2-10 mg 每单位剂量，优选约 5 mg，同时在这样的制剂中胱氨酸或谷胱甘肽或甲硫氨酸或其组合的量是 2-10 mg 每单位剂量，优选约 5 mg ；和用于在胃中释放活性剂的制剂中半胱氨酸的量是 10-50 mg 每单位剂量，优选约 20 mg，同时在这样的制剂中胱氨酸或谷胱甘肽或甲硫氨酸或其组合的量是 10-50 mg 每单位剂量，优选约 20 mg。

12. 前述权利要求中任一项的组合物，特征在于其包含稀释剂例如填充剂或膨胀剂、甜味剂例如糖或糖醇、矫味剂、润滑剂、树胶基质、非离子聚合物或离子化聚合物、或这些物质的两种或更多种的组合，作为添加剂。

13. 权利要求 12 的组合物，特征在于所述树胶基质选自天然或合成的弹性体、软化剂、蜡和脂质，天然树胶基质优选选自天然橡胶和熏制天然橡胶，和合成树胶基质优选选自丁

苯橡胶、聚乙烯和聚醋酸乙烯酯。

14. 权利要求 12 的组合物，特征在于所述非离子聚合物选自甲基纤维素 (MC)、羟丙基纤维素 (HPC) 和羟丙基甲基纤维素 (HPMC) 以及聚乙二醇 (PEG)。

15. 权利要求 12 的组合物，特征在于所述离子化聚合物选自羧甲基纤维素钠 (NaCMC)、藻酸、藻酸钠、壳聚糖、聚卡波非 (Noveon™) 和卡波姆 (Capropol™)。

16. 权利要求 12 的组合物，特征在于所述稀释剂选自乳糖、磷酸钙、淀粉、羧甲基纤维素、羟甲基纤维素。

17. 前述权利要求中任一项的组合物，特征在于其已被配制为口香糖，其中树胶基质占口香糖的 15-40%，剩余的部分包括选自药剂、糖、甜味剂、软化剂、矫味剂和着色剂的试剂。

18. 权利要求 1-16 中任一项的组合物，特征在于其已被配制为包含 40 至 80 w-% 含量的非离子大分子和 20 至 60 w-% 含量的离子化聚合物的口含片剂。

19. 权利要求 1-16 中任一项的组合物，特征在于其已被配制为包含 90 至 98 w-% 含量的稀释剂的舌下片剂。

20. 权利要求 1-16 中任一项的组合物，特征在于其已被配制为包含 10 至 50 w-% 含量的在胃中不溶的聚合物和 20 至 70 w-% 含量的膨胀剂的骨架颗粒剂或骨架片剂。

21. 前述权利要求中任一项的组合物，特征在于其通过一次将由组合物配制的 1 或 2 个制剂置于口腔中并以 4 至 10 小时的时间间隔、最优选 6 至 8 小时的时间间隔用新的制剂替换它们来给药。

22. 选自 L- 半胱氨酸、D- 半胱氨酸和 N- 乙酰基半胱氨酸的一种或多种半胱氨酸化合物与化合物胱氨酸、谷胱甘肽和甲硫氨酸中的一种或多种的组合，其用作药物。

23. 一种减少人受试者中严重头痛的发生率的方法，特征是进行以下阶段 ：

a) 提供给至少偶尔罹患严重头痛的受试者权利要求 1-20 中任一项的组合物，所述组合物与消费含乙醇饮料或食品或者含乙醛饮料或食品一起自我给予，或与吸烟一起自我给予，

b) 允许受试者自我给予所述组合物，和

c) 允许受试者吃、喝或吸烟，

由此半胱氨酸和胱氨酸或谷胱甘肽或甲硫氨酸结合伴随受试者消费饮料或食品而在体内生成的或携带到体内的乙醛，和

d) 任选地，在认为必要时，重复阶段 a) 至 c) 多次。

24. 权利要求 23 的方法，其用于减少偏头痛或丛集性头痛的发生率，或预防偏头痛或丛集性头痛。

25. 权利要求 23 或 24 的方法 ， 特征是在步骤 b) 中通过将由所述组合物配制的 1 或 2 个制剂置于口腔中或咽下它们，给予受试者所述组合物，和任选的步骤 d) 通过以 4 至 10 小时的时间间隔、最优选 6 至 8 小时的时间间隔用新的制剂替换所述制剂进行，和任选地还重复步骤 c)。

预防头痛的组合物

发明领域

[0001] 本发明涉及一种非毒性口服药用组合物，其用于减少严重头痛、特别是偏头痛或丛集性头痛的发生率，或预防严重头痛、特别是偏头痛或丛集性头痛，或至少减轻严重头痛、特别是偏头痛或丛集性头痛。此外，本发明涉及用于减少这样的严重头痛的发生率或预防这样的严重头痛的方法。

[0002] 相关领域的描述

丛集性头痛是神经性疾病，作为其最突出的特点，其涉及极度强烈的折磨人的单侧头痛。"丛集性"指这些头痛周期性地发生的倾向，伴有被自发性缓解中断的活动期。疾病的原因目前尚不知道。它影响大约 0.1% 的人群。

[0003] 虽然偏头痛诊断在女性中更常见，但丛集性头痛在男性中更流行。丛集性头痛的男女之比为约 5:1。它主要地发生在 20-50 岁的年龄之间。

[0004] 仅在芬兰，超过 15 000 人患有丛集性头痛（约 0.3 %的人群）。患有偏头痛的人的数量甚至更大（10-20 %的人群）。

[0005] 常见的疾病发作的持续时间在从短至 15 分钟到 3 小时或更长的范围内。如果不治疗，疾病发作的频率是在 48 小时内 1 至 16 次发作。头痛可伴有下面的自发症状中的一种或多种：上睑下垂（眼睑下垂）、瞳孔缩小（瞳孔收缩）、结膜充血（结膜发红）、流泪（流眼泪）、鼻液溢（鼻漏），以及不常见的面部潮红、肿胀或发汗，全部出现在与疼痛相同的头部一侧。

[0006] 头痛发作的起病快，且大多数通常没有为偏头痛特征的初步迹象。

[0007] 丛集性头痛有时被称为"闹钟头痛(alarm clock headaches)"，因为其将人从睡眠中唤醒的能力和由于其定时的规律性：个体疾病发作和丛集性二者本身可具有有节律的规律性；疾病发作的侵袭在每天早晨或晚上的精确时间是典型的，甚至精确在 1 周后的同一时间。丛集性趋向于遵循日光节约时间的变化并更经常发生在春分和秋分。这促使研究人员推测涉及大脑的"生物钟"或昼夜节律。

[0008] 在偶发性丛集性头痛中，疾病发作通常每日出现一次或多次，往往在每日的相同时间，持续数周或甚至数月的时期，接着出现持续数周、数月或数年的无头痛时期。这些发作往往发生在相同的季节，例如在秋季或春季期间。

[0009] 然而，大约 10-15% 的丛集性头痛患者是慢性的，并且他们可在数年中每日经历多次头痛。约 10% 的偶发性丛集性头痛在某一时间点转化成慢性类型。

[0010] 丛集性头痛有时分类为血管性头痛。已建议将剧烈的疼痛与造成对三叉神经的压力的血管扩张联系起来。虽然这个过程被认为是疼痛的直接原因，但病因尚不完全清楚。

[0011] 已知所述发作由诸如饮酒、睡眠习惯的改变、过度的身体劳损、怒气的爆发和压力变化（例如在飞行或登山期间）等因素触发。还已暗示在这些发作和吸烟之间存在关联。

[0012] 最后提到的痛苦通常在对吸烟严重成瘾的人中发现。还有已显示第二手烟触发丛集性头痛的病例。

[0013] 在丛集性发作 (cluster bout) 期间还出现对乙醇的过敏性。对乙醇敏感的患者

注意到疾病发作在适量乙醇摄入后 5-45 分钟内引发，所述适量乙醇通常是少于一份鸡尾酒 (a single cocktail) 或一杯酒。在 70-80 % 的暴露中，乙醇触发疾病发作。

[0014] 实验上，在发作期间通过给予硝酸甘油或组胺，可在几乎所有的患者中引发疾病发作。组胺最可能通过引发炎性反应发挥功能。

[0015] 还已显示肥大细胞（组胺在许多组织中的主要贮库）以增加的数量发现在丛集性头痛患者的疼痛颞区的皮肤中。这种效应也发现于偏头痛患者中。

[0016] 丛集性头痛是良性的，但由于与它们有关的极端和令人虚弱的疼痛，和潜在的自杀风险，严重的疾病发作仍然作为医疗紧急情况来处理。由于病况的相对稀缺性和症状的不确定性，一些患者可能不在急诊室接受治疗，和人们可能甚至会被误认为表现出觅药行为。

[0017] 存在有时被误认为丛集性头痛的其它类型的头痛，例如慢性阵发性偏头痛 (CPH) 和猝发性头痛。

[0018] 治疗丛集性头痛的药物被分类为中断性 (abortive) （例如可的松、偏头痛药物、酒石酸麦角胺、那拉曲坦、夫罗曲坦或对枕神经的局部麻醉剂）或者预防性（预防药，例如维拉帕米、锂、丙基戊酸钠、托吡酯、巴氯芬、褪黑激素、二甲麦角新碱、吲哚美辛或辣椒素）。此外，可使用短期过渡性药物（如类固醇），同时制定和调整预防性治疗。

[0019] 欧洲的指导方针提议使用钙通道阻断剂维拉帕米。也使用类固醇，例如泼尼松龙 / 泼尼松。二甲麦角新碱、锂和抗惊厥药托吡酯被推荐作为替代疗法。

[0020] 非处方的止痛药（例如阿司匹林、对乙酰氨基酚和布洛芬）通常对源自丛集性头痛的疼痛没有作用。通常基于个体的经验，在试验各种药物后，选择治疗。没有可靠的试验结果是可利用的。

[0021] 然而，本发明人已经令人惊奇地发现，减少带到人受试者体内或在人受试者体内形成的乙醛的量的药用组合物将减轻和预防这些严重头痛，特别是丛集性头痛，这可提供这些头痛和所述乙醇消费以及吸烟之间的联系。

[0022] 乙醇的第一代谢物是乙醛。乙醇均匀地分布在各器官的液相中。因此，在享用乙醇后且只要在器官中有乙醇，血液、唾液、胃液中的乙醇含量和肠中的含量是相同的。乙醛尤其通过微生物的作用由乙醇形成。微生物，尤其是在消化道中的微生物，能够将乙醇氧化为乙醛。例如，即使在中等剂量 (0.5 g/kg) 的乙醇后，在人的唾液中已发现微生物源的高乙醛含量 (18-43 μM)。换言之，乙醛积聚在唾液中作为微生物代谢的中间产物 (Homann 等，Carcinogenesis (1997) 18:1739-1743)。

[0023] 在有机体中，作为肝脏代谢的结果，以及局部地在消化道中通过微生物的乙醇脱氢酶，如此由乙醇形成乙醛 (Salaspuro 等，(1996) Ann Med 28:195-200)。唾液从口腔传播到消化道的其它区域，从而在唾液中含有的乙醛的影响区域包括口、咽、食管和胃。因此，乙醛的影响可扩展到整个上消化道区域。

[0024] 还已表明乙醛积聚在大肠中，因为大肠中的代表正常菌丛的细菌能够将乙醇转化为乙醛 (Jokelainen 等，(1996) Gut 39:100-104)。在肠中，还可发现内源性乙醇，即在肠中，在无氧条件下，在微生物的作用下形成的乙醇。例如，当该乙醇与粘膜附近的氧接触时，形成乙醛。

[0025] 在其它方面，致癌乙醛也可通过口腔微生物从各种具有高糖或碳水化合物含量的

食品内源性产生，这将引起胃中，特别是患有胃酸缺乏的患者的胃中乙醛含量亦升高。

[0026] 发明人的最近研究已表明，所有的含糖（蔗糖、麦芽糖、乳糖）食品，包括饮料，可包含显著量的乙醛(5-2000 μM)和乙醇(0.1-0.5每千(per mille))，或乙醛可在食品中形成。同样地，一些酸奶、酸乳酪和果汁包含乙醛和乙醇(PCT/FI2006/000104，通过引用结合到本文中)。

[0027] 在主动吸烟期间，唾液中的乙醛也从基础水平增加至261.4±45.5 μM的值(Salaspuro等(2004) Int J Cancer, 2004 Sep 10; 111(4):480-3)。

[0028] 现有技术公开含有结合乙醛的化合物的药用组合物，它们的作用是基于有效的物质与血液和/或细胞中的乙醛反应，例如，US 5 202 354、US 4 496 548、US 4 528 295、US 5 922 346。

[0029] 当这样的组合物被咽下时，有效的物质即刻到达小肠并从那里进入血液循环(Matsuoka，美国专利号5,202,354和Moldowan等，美国专利号4,496,548)。

[0030] 已有人提议使用包含氨基酸和维生素的制剂，其在口腔中被吸吮或咀嚼，以减少有害自由基化合物的肝介导作用，所述有害自由基化合物在使用烟草制品或暴露于烟草制品时形成。认为在被吸收后，氨基酸影响各种组织(Hersch，美国专利号5,922,346，Hersch, 国际专利申请WO 99/00106)。然而，在所有这些情况中，影响仅仅是全身的。

[0031] 出版物WO 02/36098（通过引用结合到本文中）提出使用包含游离巯基和/或氨基的化合物供局部和长期结合唾液、胃或大肠中的乙醛。所述化合物与能够使其在口腔、胃或大肠的环境下释放至少30分钟的物质混合。在这种情况下，作用限于胃肠道。

[0032] 出版物WO 2006/037848（通过引用结合到本文中）提出包含含有一个或多个游离巯基和/或氨基的化合物的组合物，供除去或减少吸烟期间唾液中的醛含量。同样这种作用仅仅是局部的。

[0033] 然而，现有技术并未提出使用半胱氨酸或胱氨酸或其它类似的化合物以缓解或预防任何类型的头痛。此外，也未开发组合产品。

[0034] 基于发明人最近的研究，乙醛在引起严重头痛、特别是丛集性头痛和偏头痛中起一定作用。由于些病症尚不能有效地预防，以及所有现有的预防药物具有严重的副作用，因此需要寻找替代和温和的方式以在患有这些严重头痛的受试者中至少减轻症状或减少发作次数。

[0035] 发明简述

本发明的一个目的是提供新的组合物，其可用于预防严重头痛，例如丛集性头痛、偏头痛、猝发性头痛或慢性阵发性偏头痛，或至少减少严重头痛，例如丛集性头痛、偏头痛、猝发性头痛或慢性阵发性偏头痛发作的发生率。

[0036] 提供用于治疗经诊断患有丛集性头痛或偏头痛的人的新的方法和用途也是本发明的一个目的。

[0037] 特别地，本发明的一个目的是提供组合物，其可用于治疗或预防严重头痛，并且其掩盖活性剂的味道。

[0038] 这些和其它目的，连同其超过已知产品和方法的优势，可通过如在此后描述的和要求保护的本发明实现。

[0039] 已表明包含一种或多种半胱氨酸作为活性剂的组合物结合乙醛。已发现这些活性

剂还能够破坏由一些微生物（特别是在胃中）形成的生物膜。还可使用包含半胱氨酸的组合物实现微生物的至少部分根除，虽然这种作用可能是生物膜破坏的结果，从而胃酸能够攻击微生物。

[0040] 所有以上提及的包含一种或多种半胱氨酸的组合物的作用已表明在具有胃酸缺乏，或低酸胃的患者（常常与幽门螺杆菌（*H. pylori*）感染有联系）中也是成功的。为了估计由胃肠道(GI道）中的乙醛造成的问题的程度，对诊断为可能的幽门螺杆菌(H. pylori)感染开始任何治疗将是值得推荐的。

[0041] 本发明的组合物可用于预防丛集性头痛(CHA)、普通偏头痛或二者，或甚至猝发性头痛或慢性阵发性偏头痛。

[0042] 因此，本发明涉及一种用于口服给予的非毒性固体药用组合物，其包含与选自胱氨酸、谷胱甘肽和甲硫氨酸的一种或多种试剂组合的选自L-半胱氨酸、D-半胱氨酸和N-乙酰基半胱氨酸的一种或多种试剂。

[0043] 更特别地，本发明的组合物的特征是在权利要求1的特征部分所述的那些。

[0044] 此外，用于依据本发明的医学应用的本发明的活性剂的特征是在权利要求22中所述的那些，和本发明的方法的特征是在权利要求23中所述的那些。

[0045] 通过本发明获得相当大的优势。因此，本发明提供在患有严重头痛、例如丛集性头痛或偏头痛的受试者中预防头痛发作或至少减少头痛发作的发生率或数目的组合物和方法。

[0046] 所述组合物对于释放食物产品或饮料（包括水或任何饮料）中的活性剂是有效的，特别是在这些食物产品或饮料包含乙醇、乙醛、酵母或糖的情况下。优选地，在这些情况下，将组合物加入到与消费（即吃或喝）有关的食物产品或饮料中。在实践中，在临吃或喝之前，将组合物加入到食物产品或饮料中。

[0047] 所述组合物亦有效用于在口腔或在胃中释放活性剂，并结合乙醛，特别是当它们连同吃或喝（即，临在吃或喝之前、在吃或喝期间或刚在吃或喝之后）或连同吸烟一起被消费时。实际上，组合物通常在受试者坐在餐桌旁之时给予，或刚刚在点燃香烟（或开始使用另一种烟草制品）之前给予，或把香烟熄灭后立即给予。

[0048] 然而，尽管这里隐含的局部效应，由于另外的选自胱氨酸、谷胱甘肽和甲硫氨酸的活性剂，因此组合物也具有全身作用。这种另外的活性剂在体内转化为半胱氨酸，但所述转化主要在所述活性剂已通过胃之后发生，从而它经由小肠转移到血流，以提供更广泛区域的作用（经由全身途径）和更宽范围的作用。

[0049] 所述组合物也可以连续的方式，例如每8-10小时后使用。组合物包含一种或多种调节活性剂释放的载体，因此产生连续的作用。

[0050] 接下来，本发明将参照附图和详细说明来更严谨地描述。

[0051] 附图简述

图1证实包含不同量的半胱氨酸的组合物对唾液的乙醛水平的影响。

[0052] 图2证实在吸烟期间唾液乙醛水平的变化。

[0053] 图3证实使用半胱氨酸结合在吸烟期间形成的乙醛。

[0054] 图4证实与使用安慰剂口香糖比较，包含L-半胱氨酸(7.5 mg)的口香糖对在吸烟期间唾液乙醛水平的影响。

[0055] 本发明优选实施方案的详述

本发明涉及一种用于口服给予的非毒性固体药用组合物，其包含选自 L- 半胱氨酸、D- 半胱氨酸和 N- 乙酰基半胱氨酸的一种或多种半胱氨酸化合物作为活性剂，组合有一种或多种另外的活性剂，所述另外的活性剂的至少一种选自胱氨酸、谷胱甘肽和甲硫氨酸，所述组合物意欲用于减少严重头痛的发生率，或甚至预防严重头痛。

[0056] 术语“半胱氨酸化合物”意指半胱氨酸，例如 L- 或 D- 半胱氨酸，或其衍生物或盐，特别是 N- 乙酰基半胱氨酸。这种主要活性剂的功能是基于可通过这种半胱氨酸化合物在胃肠道中的反应而获得的局部作用。

[0057] 提及的选自胱氨酸、谷胱甘肽和甲硫氨酸的另外活性剂的功能是基于这些活性剂被转化为半胱氨酸或提供像半胱氨酸的类似作用（尽管是全身性的）的能力。

[0058] 由于在胃肠道中活性剂的这些基团的不同反应性，部分局部和部分全身作用是可能的。主要的半胱氨酸化合物将在胃中特别与乙醛反应，而选自胱氨酸、谷胱甘肽和甲硫氨酸的另外的活性剂在反应前将主要地经由小肠转移到血流中。

[0059] 根据本发明的一个实施方案，组合物还包含作为用于降解过量的组胺的活性剂的二胺氧化酶（即，组胺酶）。

[0060] 然而，根据一个优选的实施方案，活性剂由选自 L- 半胱氨酸、D- 半胱氨酸、N- 乙酰基半胱氨酸、胱氨酸、谷胱甘肽和甲硫氨酸的氨基酸组成。

[0061] 根据另一个实施方案，维生素或类似的营养补充剂被进一步包含在组合物中。这种补充剂可以是，例如，牛磺酸化合物或普通的水溶性维生素，例如维生素 C、B_2 或 B_5（这归因于这些化合物的反应性官能团的含量），或其盐。优选地，补充剂是维生素 C 或牛磺酸的盐，例如镁或钙盐，这归因于这些盐的额外神经 - 肌肉活性。更优选补充剂是牛磺酸镁，最适合是 N- 乙酰基牛磺酸镁。本文已发现这些化合物进一步减少严重头痛的发生率，或甚至预防严重头痛。

[0062] 所述组合物可配制为，例如，片剂、胶囊、颗粒剂或散剂，或任选地配制为填充有所述散剂或颗粒剂的片剂或胶囊剂。因此，组合物可以配制为单一 (monolithic) 制剂或多元 (multiparticular) 制剂。用于在食品或饮料（包括水和任何饮料）中释放的组合物优选地以散剂或颗粒剂的形式被配制到并加入所述食品或饮料中。用于给予到受试者的口腔或胃中并在受试者的口腔或胃中释放的组合物，依次优选地作为胶囊、片剂或锭剂给予，最合适作为包封颗粒形式的活性剂和添加剂的胶囊给予。

[0063] 半胱氨酸或 N- 乙酰基 - 半胱氨酸的功能是基于在吸烟期间或在消费乙醇或含乙醇或含乙醛的食品或饮料期间形成的乙醛的中和，所述含乙醇或含乙醛的食品或饮料包括含有在临消费前或在消费后即刻能够形成乙醇或乙醛的物质（例如某些细菌、酵母或碳水化合物）的食品和饮料。

[0064] 以上提及的任选的维生素和补充剂通过增强半胱氨酸化合物的乙醛结合效应而发挥功能。

[0065] 胱氨酸、谷胱甘肽或甲硫氨酸的功能又反过来基于其在胃肠道中的低反应性，从而以其原始形式直接被引导进入小肠，在那里它将首先转化为半胱氨酸并与通过了胃携带的任何剩余的乙醛反应，其然后被带到血流并进一步到达器官，特别是肝，以排除在这些器官中形成的任何乙醛。

[0066] 二胺氧化酶（即，组胺酶）的功能是基于其在降解组胺中的酶活性，由此减少严重头痛的这种进一步的病因。

[0067] 定义

本发明的组合物包含有效量的选自 L- 半胱氨酸、D- 半胱氨酸和 N- 乙酰基半胱氨酸的一种或多种试剂，以及选自胱氨酸、谷胱甘肽和甲硫氨酸的一种或多种试剂。谷胱甘肽可以氧化的或者还原的形式存在于组合物中。优选地，使用还原的形式，因为这将提供增加的局部作用，而氧化的形式可靶向作用的全身途径。任选地，有效量的二胺氧化酶、牛磺酸化合物或普通的水溶性维生素也可包括在组合物中。

[0068] “有效量”意指能够结合或灭活存在于食品、乙醇、其它饮料或烟草中的，或在消费食品、乙醇或其它饮料期间或吃或喝之后形成的，或在吸烟期间或在吸烟后形成的一定量的乙醛的量；或至少保持乙醛含量基本上低于未使用组合物时的乙醛含量的量。在二胺氧化酶的情况下，有效量意指能够降解受试者中暂时形成的过量组胺的量。

[0069] 保持乙醛含量基本上低于未使用组合物时的乙醛含量意指与未使用依据本发明描述的组合物时的乙醛含量相比，乙醛含量应保持低至少 20%、优选地超过 40% 和最优选地超过 60% 的水平。

[0070] 提及的乙醛主要在受试者的唾液中形成。由于乙醛沉积到呼吸消化道 (aerodigestive tract)，乙醛还通过唾液的正常清洗而到达食管和胃。此外，进一步达到进入血流的乙醇将蔓延至全身并进入器官，在那里它同样地可造成损害，或者可以转化为乙醛。因此，至少至小的程度来说，危害是全身的。然而，仅全身效应或仅局部效应不排除问题。

[0071] 主要在人口腔、食管、胃或小肠或大肠，和在小的程度上在身体的其它区域的这样的有害含量的乙醛，可伴随以下形成：消费含乙醇饮料特别是强烈的乙醇饮料，或含乙醇的食品，或作为吸烟的后果，或当消费含乙醛的产品时，特别是在患有萎缩性胃炎或胃酸缺乏的人中。

[0072] ″乙醇饮料″是含乙醇的饮料，它们的乙醇含量在 0.7% 体积和 84% 体积内变化。

[0073] ″乙醇食品″指包含至少 0.7% 乙醇的食品。这样的食品可以是，例如，发酵果汁或果酱，或用少量的乙醇保存的食品，糕点、果冻和用利口酒调味的慕斯或相应的含乙醇产品。

[0074] “含乙醛食品”指包含乙醛的食品。乙醛被包含在食品中，其中乙醇的生成与发酵有关，例如啤酒、苹果酒 (cider)、葡萄酒、家酿的啤酒和其它乙醇饮料，以及许多果汁。在某些食品中，例如一些乳制品，乙醛用于保存的目的，并增加味道，或乙醛是作为微生物活动的结果在产品中形成的。例如，含糖果汁或含糖食品一般来说为这样的微生物提供食物底物。例如，在发酵的乳制品，例如酸乳酪中形成高浓度的乙醛。用来制备酸乳酪的微生物在酸乳酪中产生乙醛。至于乙醇饮料，雪利酒和苹果白兰地酒含有特别大量的乙醛。

[0075] 依据本发明的组合物的应用可具有甚至与消费轻乙醇饮料或食品有关的益处，这些饮料或食品仅包含少量的乙醇。

[0076] ″与消费乙醇饮料相关″在此指从受试者开始消费乙醇饮料时起始至受试者血液中不再有乙醇时为止的时间段。然而，同样地这个术语并不意欲限制本发明至血液中的乙醇反应。

[0077] 由于本发明的组合物“与消费饮料相关”也可以是有益的，其中饮料包含能够在受试者体内形成乙醇或乙醛的物质，或仅包含少量的乙醇（因此在血液中不形成可检测的乙醇含量），因此所述时间段可任选地被解释为在受试者喝之前 10-0 分钟开始至喝下后约 10 分钟为止。

[0078] 类似地，“与吃相关”在此指在受试者进食之前 10 分钟开始至吃完后 10 分钟为止的时间段。

[0079] 所述组合物可例如与食品混合，或它可在进食之前或之后给予。

[0080] 同样“吸烟”应指通过吸入使用烟草制品，例如吸入香烟、雪茄或烟斗。然而，烟草可例如通过吸烟、嚼烟 (chewing)、湿烟 (wetting) 或闻烟 (snuffing) 使用，“烟草制品”指任何烟草制品，例如香烟、雪茄、烟斗、鼻吸或咀嚼的烟草。因此，″与吸烟相关″在此指在从开始使用烟草到当所述使用停止时为止的时间段期间对烟草制品的任何使用。

[0081] 然而，根据发明人的研究，特别是吸烟，似乎造成乙醛在口腔中的形成。

[0082] 本发明的组合物

本发明的组合物包含与选自胱氨酸、谷胱甘肽和甲硫氨酸的一种或多种试剂组合的选自 L- 半胱氨酸、D- 半胱氨酸和 N- 乙酰基半胱氨酸的一种或多种试剂，作为活性剂，其呈任何前述的形式，所述组合物任选地包含另外的活性剂。

[0083] 根据本发明的一个实施方案，组合物还包含二胺氧化酶（即组胺酶），作为用于降解过量的组胺的活性剂。

[0084] 根据另一个实施方案，牛磺酸化合物或普通的水溶性维生素被包含在组合物中。

[0085] 所述组合物还包含一种或多种药用添加剂，优选地包括一或多种提供所述化合物在身体的所需部位控制释放的非毒性载体。

[0086] 控制释放在此意指半胱氨酸化合物的局部释放，在口腔的环境下在至少 5 分钟期间，优选在 5-15 分钟期间释放；或在胃的环境下在至少 30 分钟期间， 优选在 0.5-8 小时期间释放，同时胱氨酸或谷胱甘肽或甲硫氨酸直接引导进入小肠供释放进入血流。

[0087] 依据本发明，从乙醛结合活性剂获得的产品对有机体是安全的和非毒性的。

[0088] 除了半胱氨酸及其衍生物以及胱氨酸、谷胱甘肽和甲硫氨酸外，本发明的范围还包括这些化合物的盐，特别是药学上可接受的盐，特别是水溶性盐。

[0089] 进一步将选自以下的至少一种物质加入到本发明的组合物中具有优势：铬、维生素 B12、A-、D-、E、-C- 维生素、烟酸、生物素、硫胺、B2-、B5-、B6- 维生素和叶酸和微量元素，例如铬、锰、硒、锌和铁，和降低乙醛形成的抗微生物剂，因为这些物质进一步改进所需效果。如上所述，维生素 C、B2 和 B5 是特别有用的，尤其是维生素 C。

[0090] 加入到本发明的组合物中的另一种有用化合物还有卵磷脂，其可简化组合物的乙醛 - 结合作用。

[0091] 然而，仅仅为无毒性的并适合于人消费的这些化合物（并以这些量），适用于根据本发明的组合物。

[0092] 根据本发明的组合物的单位剂量可呈现为例如，散剂、片剂、胶囊、锭剂或口香糖的形式。可能使用的片剂可呈现为单一或多元制剂的形式，而可能使用的胶囊可包含呈例如散剂或颗粒剂形式的活性剂和添加剂。最适合地，将本发明的组合物配制为包含活性剂以及一种或多种合适的添加剂（最适合呈颗粒形式）的胶囊。

[0093] 颗粒、片剂和胶囊可用水溶性薄膜覆盖，其有效地覆盖或掩盖活性剂的味道。

[0094] 意欲在食品或饮料中释放的所述组合物，在消费前，可被配制为例如散剂，其容易地混合在食品或饮料中。

[0095] 在这样的散剂的情况下，组合物中的活性剂的含量可在 0.2-2 w-% 半胱氨酸和 0.2-2 w-% 胱氨酸或谷胱甘肽或其组合之间变化。添加剂典型地包括掩盖活性剂的味道的试剂，例如甜味剂或矫味剂。

[0096] 意欲在口腔释放的组合物可被配制为例如片剂或其它制剂，其可置于颊或唇和齿龈之间，或为在口腔中吮吸或咀嚼的制剂。

[0097] 依据最简单的选择，用于在口腔中释放的单位剂量可通过将固体物质（任选地用乙醇湿润）简单地混合，并将它们配制为合适的形式，例如压制成片剂来制备。

[0098] 意欲在胃中释放的组合物可被配制为例如待吞咽的片剂或胶囊。

[0099] 在口香糖的情况下，组合物中的活性剂的含量可在 0.2-2 w-% 的半胱氨酸和 0.2-2 w-% 的胱氨酸、谷胱甘肽或甲硫氨酸或其组合之间变化。

[0100] 在这种情况下，组合物还包含树胶基质，其含量为所述组合物的 90 至 99 w-%，优选地为每单位剂量 500-1500 mg 的量。

[0101] 在要保持在口腔中的锭剂或片剂的情况下，所述组合物中的活性剂的含量可在 0.3-20 w-% 的半胱氨酸和 0.3-20 w-% 的胱氨酸、谷胱甘肽或甲硫氨酸或其组合之间变化。

[0102] 在这种情况下，组合物还包含一种或多种稀释剂或填充剂，其含量为所述组合物的 85-98 w-%, 优选地为每单位剂量 50-750 mg 的量。

[0103] 在待吞咽的片剂或胶囊的情况下，所述组合物中的活性剂的含量可在 0.5-20 w-% 的半胱氨酸和 0.5-20 w-% 的胱氨酸、谷胱甘肽或甲硫氨酸或其组合之间变化。

[0104] 在这些情况下，组合物还包含一种或多种膨胀剂，其含量为所述组合物的 85-98 w-%，优选地为每单位剂量 50-750 mg 的量。

[0105] 所有类型的制剂优选地包含每单位剂量 2-50 mg 的量的半胱氨酸，和每单位剂量 2-50 mg 的量的胱氨酸、谷胱甘肽或甲硫氨酸或其组合。

[0106] 根据一个优选的实施方案，组合物包含的活性剂，特别是半胱氨酸化合物和另外的活性剂的总量是 2-100 mg 每单位剂量，优选地 2-50 mg 每单位剂量，更优选地 4-20 mg 每单位剂量，和最优选 5-10 mg 每单位剂量。

[0107] 由于半胱氨酸的局部区域的作用，仅需要很少的量 / 剂量，由此半胱氨酸不以任何明显的程度稀释，且由于活性剂的协同作用，半胱氨酸和胱氨酸或谷胱甘肽或甲硫氨酸二者减轻受试者的头痛并因此同时经由几种途径提供头痛的减少的发生率。这提供令人惊奇的强烈效果。

[0108] 在口腔的环境下活性化合物的释放通常以每小时 15-25 mg 的量发生。在胃中，释放速率通常为每小时 40-80 mg。

[0109] 依据本发明的 1 或 2 个制剂可在某一时间给予并可在 2 至 10 小时间隔，最优选地在 4 至 8 小时间隔重复给予。在口香糖的情况下，可采用 6-10 小时的较长时间间隔，因为一个口香糖，在咀嚼后，可塞在颊和牙龈之间，并在再次咀嚼后释放更多的活性剂。

[0110] 可配制所述组合物在口腔或在胃中以控制的方式释放其活性剂。

[0111] 根据本发明的一个优选的实施方案，所述组合物将在口腔中释放活性剂，并且包

含为控制释放目的的载体，所述载体通常呈聚合物的形式，其在口腔中是不溶的或仅微溶（此后称为“在口腔中不溶的载体 / 聚合物”）。

[0112] 在口腔中不溶的聚合物可以是任何药学上可接受的添加剂，例如甲基丙烯酸酯聚合物，例如丙烯酸树脂 (Eudragit) RS 或 S，或乙基纤维素 (EC)。

[0113] 载体也可选自形成粘附在口腔粘膜的凝胶的那些。这样的载体通常选自药学上可接受的聚合物。更特别地，载体可选自各种壳聚糖、藻酸盐例如藻酸钠、氢氧化铝、碳酸氢钠、羧甲基纤维素钠和碳酸氢钠。

[0114] 除了活性剂和任选的载体外，组合物可包含，例如：

1. 药学上可接受的稀释剂（填充剂、膨胀剂），
2. 甜味剂，例如糖和糖醇，
3. 矫味剂，和
4. 助滑剂 (Slip additives)/ 润滑剂。

[0115] 糖可包含，例如，蔗糖、果糖和葡萄糖或其混合物。糖醇可包含甘露醇、山梨醇、麦芽糖醇、乳糖醇、异麦芽糖醇 (isomalt) 或木糖醇或其混合物。优选地，所用的添加剂不与所述组合物中的其它成分反应。不要太甜，优选的甜味剂包含甘露醇，且其在所述组合物中的量可以相当大；因此，它同时作为稀释剂发挥作用。

[0116] 矫味剂可包含，例如，绿薄荷、薄荷、薄荷醇、柑橘类水果、桉树或茴香子或其混合物。

[0117] 所述组合物还可包含其它成分，例如防止不良的口腔异味的物质、起口气清新剂和 / 或预防龋齿功能的物质，或所述制剂可包含维生素。组合物还可包含增加唾液分泌的物质。

[0118] 此外，组合物可包含膨胀剂，优选惰性试剂，作为另外的添加剂，其含量特别为 20 至 70 w-%，优选地 40 至 60 w-%，最优选地约 50 w-%。

[0119] 惰性膨胀剂可以是例如磷酸氢二钙、微晶纤维素 (MCC)，或另一种相应的非膨胀剂。

[0120] 根据本发明的优选的实施方案，用于在口腔中释放的典型的制剂 / 单位剂量（例如一粒片剂）可包含以下成分或由以下成分组成：

半胱氨酸	2-10 mg
胱氨酸 / 谷胱甘肽 / 甲硫氨酸	2-10 mg
稀释剂 / 甜味剂	50-750 mg
矫味剂	适量
润滑剂 (0.5-3% 重量)	5-25 mg

所述片剂可通过任何熟知的方法，将粉末状的物质混合并将其压制成吮吸片剂 (sucking tablet) 来制备。

[0121] 如果增加半胱氨酸或胱氨酸或谷胱甘肽或甲硫氨酸的量，则稀释剂 / 甜味剂和矫味剂的量也可增加，因为优选掩饰半胱氨酸的味道。

[0122] 一种典型的制剂 / 单位剂量可被配制为口香糖，并基本包含以下成分或由以下成分组成：

半胱氨酸	2-10 mg

胱氨酸 / 谷胱甘肽 / 甲硫氨酸 2-10 mg

树胶基质

（包含例如甜味剂） 500-1500 mg

矫味剂 适量

润滑剂 (0.5-3% 重量） 5-30 mg

树胶基质可由加药的口香糖 (Morjaria, Y. 等, Drug Delivery Systems & Sciences, vol. 4, No. 1, 2004) 或天然或合成的弹性体、软化剂、蜡或脂质形成。天然树胶基质，包括天然橡胶和熏制天然橡胶，为 FDA 许可的。然而，现代树胶基质通常是合成的，并且包括丁苯橡胶、聚乙烯和聚醋酸乙烯酯。

[0123] 树胶基质一般占口香糖的 15-40 w-%。剩余的部分主要包括药剂、糖、甜味剂、软化剂、矫味剂和着色剂。

[0124] 大多数基于口香糖的药物传递系统使用常规方法制备。然而，可直接压制的粉末树胶基质是对含药口香糖的最新替代。Pharmagum 是可压缩的新树胶系统。它是多元醇和 / 或糖与树胶基质的混合物。包含 Pharmagum 树胶的制剂可通过使用常规压片机压制成树胶片。制备方法快速且便宜。树胶基质（包含甜味剂）在制剂中的量可以是 50-500 mg，优选 500-1500 mg。

[0125] Pharmagum S 包含橡胶基质和山梨醇，Pharmagum M 包含橡胶基质、甘露醇和异麦芽糖醇。

[0126] 所述组合物可通过将粉末状物质混合并将其压制成可咀嚼片 (chewable piece) 来制备。

[0127] 所述制剂可以是口含片剂 (buccal tablet)，其包含：

半胱氨酸 2-10 mg

胱氨酸 / 谷胱甘肽 / 甲硫氨酸 2-10 mg

非离子大分子 5-25 mg

离子化大分子 2-10 mg

矫味剂 适量

润滑剂 0.5-3% 重量

非离子大分子包括，例如，甲基纤维素 (MC)、羟丙基纤维素 (HPC) 和羟丙基甲基纤维素 (HPMC)，和聚乙二醇 (PEG)。离子化聚合物包括，例如，羧甲基纤维素钠 (NaCMC)、藻酸、藻酸钠、壳聚糖、聚卡波非 (Noveon™) 和卡波姆 (Capropol™)。

[0128] 非离子大分子通常占口含片剂的 40-80 w-%，其中离子化聚合物通常占这样的片剂的 20-60 w-%。

[0129] 所述制剂也可以是舌下片剂 (sublingual tablet)，其基本上包含以下成分或由以下成分组成：

半胱氨酸 2-10 mg

胱氨酸 / 谷胱甘肽 / 甲硫氨酸 2-10 mg

稀释剂 / 适量甜味剂 50-500 mg

矫味剂 适量

润滑剂 0.5-3% 重量

稀释剂包括，例如，乳糖、磷酸钙、淀粉、羧甲基纤维素、羟甲基纤维素。甜味剂可以是，例如，甘露醇或木糖醇。

[0130] 稀释剂通常占舌下片剂的 90-98 w-%。

[0131] 根据本发明的另一个优选的实施方案，配制所述组合物以在胃中释放活性剂，并且包含为控制释放目的的载体，例如在胃中是不溶的或仅微溶的聚合物（在此简单地称为“在胃中不溶的载体 / 聚合物”）。为此目的，组合物优选地通过将其压制成片剂或通过将所述组合物封装入胶囊中来配制。作为选择，所述组合物可用水不溶性薄膜覆盖。

[0132] 在胃中不溶的载体可以是聚合物，例如甲基丙烯酸酯聚合物，例如丙烯酸树脂 (Eudragit) RS 或 S，或乙基纤维素。

[0133] 这样的聚合物优选地以整个组合物的 10-50 w-%，更优选 20-40 w-%， 最适合 20-30 w-% 的含量存在。

[0134] 载体也可在胃中形成漂浮在胃内容物中的凝胶，或组合物可被配制为口服的液体制剂（混合物），其物理结构优选地为凝胶。作为选择，所述组合物的载体可附着于胃的粘膜，因此造成整个制剂（包括活性剂）附着于粘膜。

[0135] 所述组合物还可包含膨胀剂， 优选惰性试剂，例如磷酸氢二钙、微晶纤维素 (MCC)，或另一种相应的非膨胀剂，例如其含量为整个组合物的 20-70 w-%，优选地 40-60 w-%，最优选约 50 w-%。

[0136] 根据本发明的一个优选的实施方案，所述组合物包含在胃中不溶的骨架颗粒剂。这样的组合物可包含例如：

半胱氨酸	5-40 w-% （优选地 25 w-%）
胱氨酸 / 谷胱甘肽 / 甲硫氨酸	5-40 w-% （优选地 25 w-%）
在胃中不溶的聚合物	10-50 w-% （优选地 20-30 w-%）
惰性膨胀剂	20-70 w-% （优选地 40-60 w-%）
乙醇	适量

在胃中不溶的聚合物在上述组合物中可为任何常用的添加剂，例如甲基丙烯酸酯聚合物，例如丙烯酸树脂 (Eudragit) RS 或 S，或乙基纤维素 (EC)。惰性膨胀剂可以是例如磷酸氢二钙、微晶纤维素 (MCC)，或其它相应的非膨胀剂。混合固体物质并用乙醇湿润。通过使用制药工业熟知的方法和装置将湿润的混合物制粒。同样可使用干燥的颗粒，或将其分配到多个剂量，例如分配到胶囊中。

[0137] 根据本发明的另一个优选的实施方案，所述组合物包括在胃中不溶的骨架片剂。这样的组合物可包含例如：

半胱氨酸	5-40 w-% （优选地 25 w-%）
胱氨酸 / 谷胱甘肽 / 甲硫氨酸	5-40 w-% （优选地 25 w-%）
在胃中不溶的聚合物	10-50 w-% （优选地 20-30 w-%）
惰性膨胀剂	20-70 w-% （优选地 20-50 w-%）

在胃中不溶的聚合物在上述组合物中可为制药工业中的任何常用的添加剂，例如甲基丙烯酸酯聚合物，例如丙烯酸树脂 (Eudragit) RS 或 S，或乙基纤维素 (EC)。惰性膨胀剂可以是，例如，磷酸氢二钙、微晶纤维素 (MCC)，或另一种相应的非膨胀剂。混合固体物质并通过使用例如乙醇或亲水性聚合物溶液将该混合物制粒。使用制药工业熟知的方法和装置将

颗粒压制成片剂。活性化合物的释放在此基于水溶性有效的化合物从片剂骨架所形成的孔隙扩散。

[0138] 根据本发明的另一个优选的实施方案，所述组合物包含一种或多种用于将制剂包衣的多孔薄膜形成剂，例如乙基纤维素或羟丙基甲基纤维素，或其组合。最适合使用乙基纤维素和羟丙基甲基纤维素的组合，例如具有 EC 对 HPMC 的相对量为 3/2-7/3 的组合。

[0139] 这样的用多孔薄膜覆盖的组合物可包含，例如：

半胱氨酸	1-50 w-% （优选地 20-50 w-%）
胱氨酸 / 谷胱甘肽 / 甲硫氨酸	1-50 w-% （优选地 20-50 w-%）
水溶性膨胀剂	50-80 w-% （优选地 30-60 w-%）
多孔薄膜形成剂	适量

在这样的组合物中，水溶性膨胀剂可以是例如乳糖或通常用于制药工业的一些其它水溶性膨胀剂。混合固体物质并使用制药工业中熟知的方法和装置将混合物压制成片剂。多孔薄膜可从水溶性聚合物，例如羟丙基甲基纤维素 (HPMC)，或水 - 不溶性聚合物，例如乙基纤维素 (EC) 制备，优选自所述聚合物的混合物制备。薄膜形成物质，例如 EC 和 HPMC 的相对量，优选地为 2-5 份不溶于水的聚合物和 1-2 份水溶性聚合物。在胃的环境下，水溶性聚合物溶解并在剩余的不溶于水的聚合物中形成孔。有效的化合物的释放在此基于水溶性的有效化合物从薄膜中形成的孔中扩散。薄膜形成物质还有效地掩蔽活性剂的味道。

[0140] 治疗

将包含有效量的半胱氨酸和胱氨酸或谷胱甘肽或甲硫氨酸的组合物加入到不久将被受试者消费的食品或饮料中，或以合适的量直接给予受试者，所述组合物可包含，例如，0.2-20 w-% 的半胱氨酸和 0.02-20 w-% 的胱氨酸或谷胱甘肽或甲硫氨酸或其组合，最适合直接给予与受试者消费的含乙醇的饮料或食品、或含乙醛的饮料或食品相关的受试者，或与受试者吸烟相关的受试者。

[0141] 此外，优选制剂具有使其容易保持在口腔或容易吞咽的形状。然而，如果用于在胃中释放活性剂的所述组合物以直径至少 7 mm，优选地 8-15 mm, 更优选地 11-15 mm 的制剂的形式呈现，则具有优势。这有助于制剂停留在胃中足够的时间以供控制释放活性剂。

[0142] 因此，本发明提供制剂和方法，其可用于减少严重头痛，特别是丛集性头痛和偏头痛的发生率。

[0143] 例如，严重头痛的发生率可使用包括以下阶段的治疗方法减少：

a) 给至少偶然患有严重头痛的人受试者提供包含半胱氨酸和胱氨酸或谷胱甘肽或甲硫氨酸的组合物，其与消费乙醇饮料或食品，或含乙醛的饮料或食品一起给予，或与吸烟一起给予，

b) 受试者自我给予所述组合物，和

c) 允许受试者吃、喝或吸烟，

由此半胱氨酸和胱氨酸或谷胱甘肽或甲硫氨酸结合与消费饮料或食品有关的生成的或带到体内的乙醛，和

d) 任选地，在感觉必要时，重复阶段 a) 至 c) 多次。

[0144] 本发明的其它应用

根据本发明的一个实施方案，将本发明的组合物给予除了患有所述严重头痛，还患有

萎缩性胃炎的人受试者。

[0145] 萎缩性胃炎尤其提高维生素 12 的吸收不良的风险，和可能导致恶性贫血。微量营养素的吸收不良可导致中枢神经系统的严重继发性疾病和骨质疏松症。患有胃体萎缩性胃炎的人群的一半可具有异常低的维生素 B12 水平，并且这些人群的至少一半同时具有增加的同型半胱氨酸的血清水平。因此，本发明的组合物（补充有维生素 B12）特别适合于给这样的人使用。维生素B12 将与其它活性剂一起释放并与至少一部分胱氨酸或谷胱甘肽或其组合一起被带到血流供发挥系统效应。

[0146] 维生素 B12 缺乏是神经退行性疾病，例如痴呆、抑郁症和多发性神经病的强风险因子。维生素 B12 的缺乏为高同型半胱氨酸血症的一个常见的原因，其是动脉硬化症、中风和心脏病发作的独立风险因子。因为胃体萎缩 (corpus atrophy) 和不良的饮食，甚至 15% 的年龄超过 50 岁的个体患有可预防的维生素 B12 缺乏的流行病。

[0147] 随着通过对合适的生物标记物的常规筛查，例如通过 GastroPanel® 筛查来早期检测胃体萎缩，和随后的治疗，可预防可能的神经失能（例如痴呆、抑郁症和多发性神经病）和血管性疾病（例如中风和心脏病发作）。人口的不断老龄化增加对筛选所述生物标记物例如通过 GastroPanel® 检查和筛选的需要，和换言之，增加对诊断萎缩性胃炎及相关风险和疾病的需要。

[0148] 除了维生素 B12 之外，其它维生素也可加入到本发明的组合物中，例如维生素 A、D、E 和 C、烟酸、生物素、硫胺、B2、B5、B6 和叶酸以及微量元素，例如铬、锰、硒、锌和铁。亚铁化合物具有特殊的优点，因为萎缩性胃炎往往与缺铁性贫血相联系。

[0149] 根据本发明的一个实施方案，在上述治疗之前先进行关于可能的幽门螺杆菌感染的诊断，优选地使用可靠地提供还关于萎缩性胃炎的诊断的测试。因此，可估计由胃肠道 (GI 道）中的乙醛引起的问题的程度。

[0150] 从文献中清楚地得知，生物标记物胃蛋白酶原 I 和 II (PG-I 和 PG-II) 以及胃泌素 -17 (G-17) 精确地测定萎缩性胃炎，一般地说可能甚至比胃镜更准确。PG I/PG II 的比率还与食管中癌变前和癌变化的出现有关。这些生物标记物被分泌到胃腔中，且少量被转移到循环中，在那里它们反映了在胃中的浓度。

[0151] PGI 的水平和 PGI/PGII 比率为胃体粘膜的功能和结构的标记物，并且 G-17 的水平，其通常在空腹血液样品中测量，是窦粘膜的功能和结构的标记物。包括例如幽门螺杆菌抗体，例如幽门螺杆菌 IgG 和 IgA，作为测试中的生物标记物，将提供还关于可能的幽门螺杆菌感染的信息。因此，所述生物标记物 (PG-I、PG-II 和它们的比率结合 G-17 和幽门螺杆菌 IgG 和 IgA) 相互补充，从而形成一个诊断面板 (panel)。

[0152] 这些生物标记物的水平优选地使用 ELISA 分析对患者的血液、血浆或血清样品，特别是对空腹血浆样品进行测定。如果具有幽门螺杆菌感染和低水平的 G-17 的患者不想要具有侵袭性的胃镜检查，胃窦的萎缩性胃炎可通过测定蛋白 - 刺激的 G-17 在血浆中的浓度加上所述得自空腹血浆样品的检查得到证实或排除。特别适合于所述目的的检查程序是 GastroPanel® 检查。

[0153] PG-I 作为萎缩性胃炎的标记物的作用是熟知的。近来还已提供关于其在确定特别是胃体粘膜的病况中的有用性的证据。

[0154] 最近已表明 PGI/PGII 比率随着胃体萎缩性胃炎的评级的增加呈线性降低。当胃

体萎缩性胃炎是晚期（中度或严重）时，比率为< 3.0。已表明当PGI/PGII比率低时，胃癌的风险增加(5-倍)。

[0155] 测量酰胺化肽激素胃泌素-17的作用虽然比胃蛋白酶原研究较少，但已经有相当的临床益处。在胃中，胃泌素-17具有刺激盐酸分泌的任务。同样的，存在一个负反馈控制，以至于盐酸抑制G-17的形成。

[0156] 结合G-17测定与PG I和II的测定，有助于将其中萎缩性胃炎(AG)限于胃底和胃体区域的病例(PG-I是低的，但G-17是高的）与其中还影响到胃窦的病例(PG-I和G-17二者是低的）区分开。这样的区别在临床上是重要的，因为后者（全身萎缩）意味着最高的已知的胃癌风险。

[0157] 为了进一步加强检查，空腹G-17分析可以与由蛋白膳食刺激后的测定进行比较。如果低G-17水平不被这样的刺激作用明显地提高，则提供了胃窦区域萎缩的很好的证据。然而，如果最初的低G-17水平通过这样的刺激作用而明显地提高，则胃窦很可能是有生理功能的，并且低的静止G-17水平（如，低于2 pmol/L)在此类病例中是胃中异常高的酸度的强烈指征，在所述病例中Barrett′s食管的风险升高。相反地，空腹G-17的生理学上的高水平是低胃酸或胃酸缺乏的强烈指征，其可由限于胃体区域的AG引起，或确实由PPI治疗引起。

[0158] 包括以下实施例仅为举例说明的目的，并不意欲限制本发明。

实施例

[0159] 实施例1——吮吸片剂的制备

制备吮吸片剂，一种类型包含：

L-半胱氨酸	20 mg
胱氨酸	20 mg
甘露醇（或等量的糖或糖醇）	750 mg
矫味剂	适量
硬脂酸镁	10 mg

另外的组合物的半胱氨酸含量有变化，其为1.25 mg、2.5 mg、5 mg和10 mg半胱氨酸。

[0160] 所述组合物通过将粉末状的物质混合并将其压制成吮吸片剂来制备。

[0161] 实施例2——口香糖的制备

制备口香糖，其包含：

半胱氨酸	20 mg
胱氨酸	20 mg
Pharmagum S、M或C	1000 mg
矫味剂	适量
硬脂酸镁	20 mg

所述组合物通过将粉末状的物质混合并将其压制成口香糖来制备。

[0162] 制备另一种组合物，其包含500 mg Pharmagum S或M和20 mg硬脂酸镁。

[0163] 实施例3——口含片剂的制备

制备口含片剂，其包含：

半胱氨酸	20 mg
胱氨酸	20 mg
Methocel	25 mg
Carbopol	7 mg
矫味剂	适量
硬脂酸镁	2 mg

所述组合物通过将粉末状的物质混合并将其压制成口含片剂来制备。

[0164] 实施例 4——舌下片剂的制备

制备舌下片剂，其包含：

半胱氨酸	10 mg
胱氨酸	10 mg
甘露醇	250 mg
矫味剂	适量
硬脂酸镁	5 mg

所述组合物通过将粉末状的物质混合并将其压制成舌下片剂来制备。

[0165] 实施例 5——所述组合物对乙醛水平的作用

5 位吸烟者（年龄 29 ± 2.8）参与了研究，其中 3 根香烟被抽吸（在之间有净化周期）。在抽吸每根香烟时（在 5 分钟时间内），志愿者吮吸各种盲片，其分别包含安慰剂、1.25 mg、2.5 mg、5 mg、10 mg 或 20 mg 的 L- 半胱氨酸。从开始吸烟 0、5、10、20 分钟后通过气相色谱分析唾液样品中的乙醛。

[0166] L- 半胱氨酸片剂（5 mg、10 和 20 mg）从唾液除去源自烟草的所有乙醛（见图 1）。使用安慰剂和 5 mg、10 mg 和 20 mg L- 半胱氨酸片剂，在吸烟后即刻的平均唾液乙醛含量分别是 191.2 ± 48.5 μM、0 μM、0 μM、0 μM。

[0167] 该研究表明甚至 5 mg 的 L- 半胱氨酸，当溶片递送时，完全灭活在吸烟期间唾液中的致癌乙醛。与安慰剂比较，1.25 mg 的 L- 半胱氨酸片剂减少约三分之二的乙醛量。

[0168] 实施例 6——吸烟和饮酒后唾液乙醛水平增加

烟草的烟雾包含乙醛，其在吸烟期间变成溶于唾液（见图 2）。在该研究中，吸烟者和非 - 吸烟者均首先饮下小剂量的乙醇，此后吸烟者抽吸 6 根香烟，每根约 5 分钟。在吸烟期间，唾液的乙醛显著超过致癌水平。

[0169] 经过吞咽，来自乙醇或者吸烟的唾液乙醛从口腔分布到咽、食管和胃。因此，致癌作用不限于口。

[0170] 用 ALDH2- 缺乏的亚洲人进行的研究提供了乙醛的局部致癌作用的最强烈的证据，ALDH2- 缺乏的亚洲人形成用于长期乙醛暴露的异常人“敲除模型（knock-out model）”。

[0171] 在患有 ALDH2- 缺乏的受试者（Flushers）中，另外的唾液乙醛似乎来自唾液腺。

[0172] 在几项来自亚洲国家的流行病学研究中，一致表明 ALDH2- 缺乏与超过 10 倍的上消化道癌风险相关。这种相关在酗酒者中是最强的，但是另外在正常的乙醇消费者中也是显著的。因此，吸烟者也明显地面临高风险。

[0173] 总之，源自烟草的乙醛似乎在上消化道作为局部致癌物以剂量依赖和协同方式起作用。

[0174] 实施例 7——使用半胱氨酸排除乙醛

半胱氨酸是含硫氨基酸。其平均摄入量是约 1g/ 天。半胱氨酸与乙醛缩合并从而经形成 2- 甲基 - 噻唑烷 -4- 甲酸 (MTCA) 使反应性的和致癌的乙醛失活。

[0175] 例如，包含少至 5mg L- 或 D- 半胱氨酸的锭剂全部排除在吸烟期间来自唾液的乙醛 (图 3)。

[0176] 反应性乙醛的有害作用可通过使其结合于半胱氨酸得到预防。这种半必需氨基酸通过非 - 酶结合，形成更稳定的化合物 2- 甲基噻唑烷 -4- 甲酸使乙醛失活。例如，已开发包含 L- 半胱氨酸的片剂和口香糖以消除在吸烟期间的乙醛暴露 (图 4)。

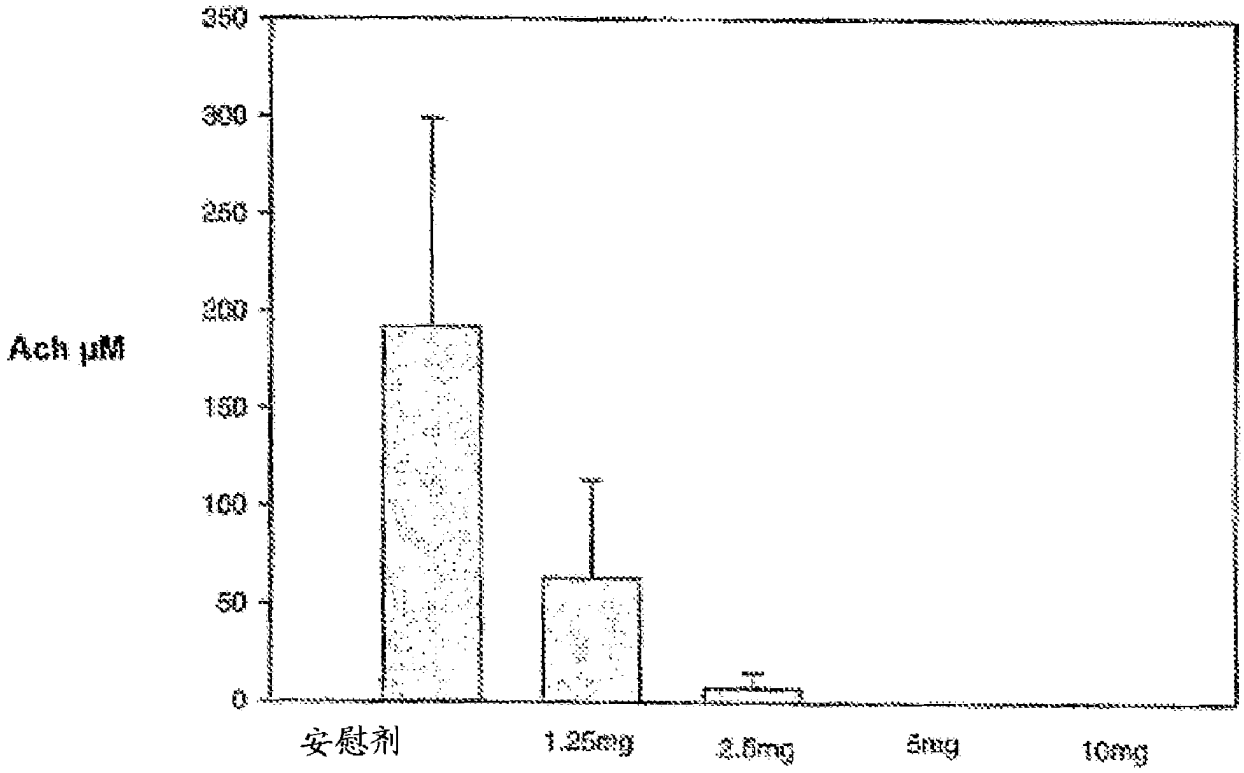
Ach μM
250
300
250
200
150
100
50
0
安慰剂
1.25mg
2.5mg
5mg
10mg
L-半胱氨酸含量

图 1

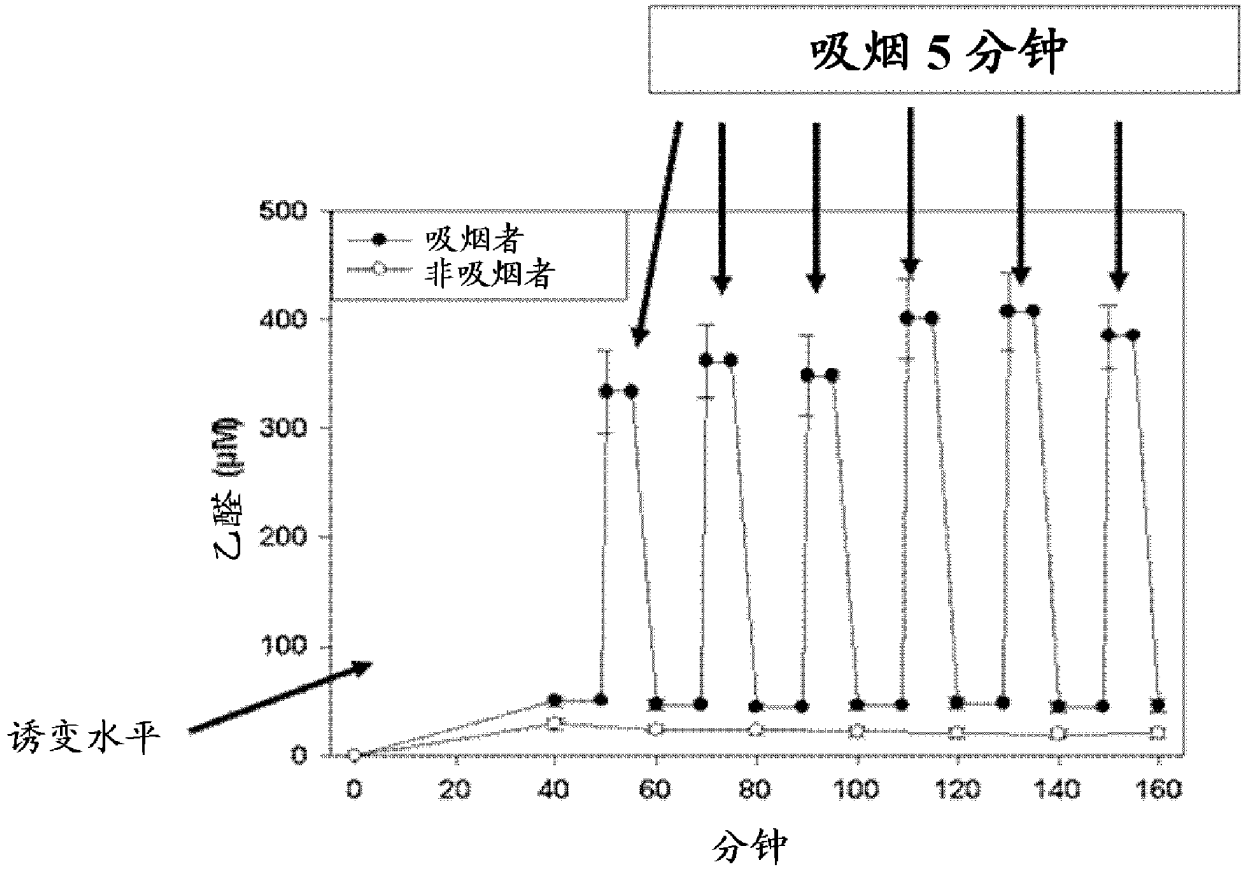
吸烟 5 分钟
吸烟者
非吸烟者
乙醛 (μM)
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
分钟
诱变水平

图 2

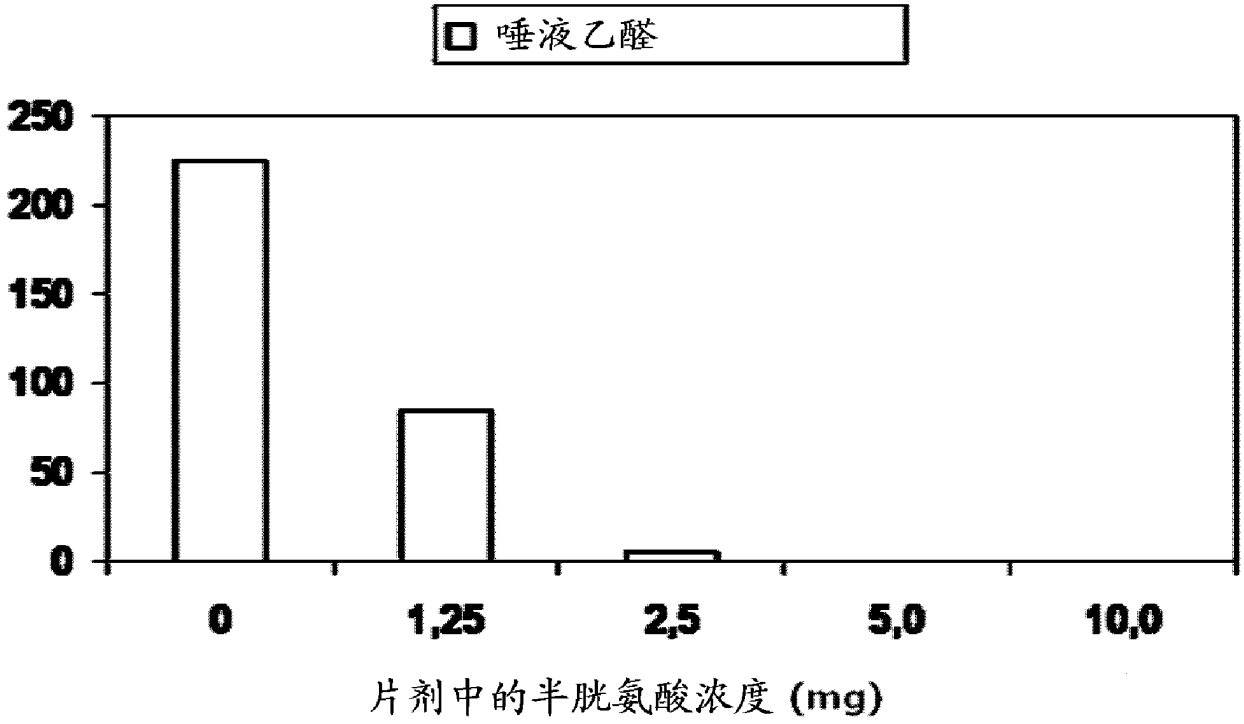
唾液乙醛
250
200
150
100
50
0
0
1,25
2,5
5,0
10,0
片剂中的半胱氨酸浓度 (mg)

图 3

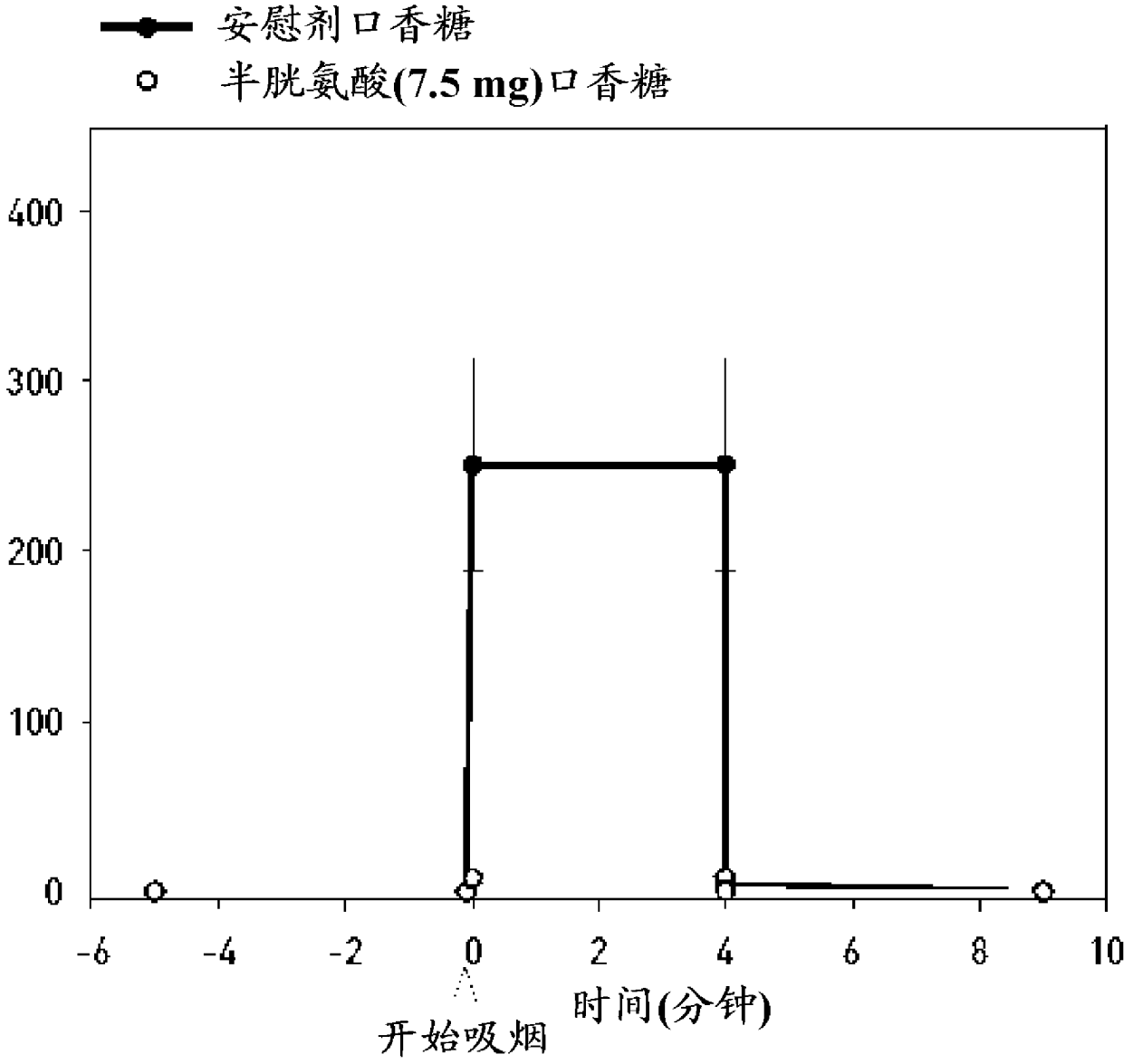

图 4