Title: COMPOSITION FOR PREVENTING HANGOVER SYMPTOMS

Abstract: The present invention concerns a non-toxic solid pharmaceutical composition for oral administration for use in preventing hangover symptoms, wherein the composition contains one or more cysteine compounds from the group of L-cysteine, D-cysteine and N-acetyl-cysteine, combined with one or more additives, and optionally a combination of B-vitamins.
COMPOSITION FOR PREVENTING HANGOVER SYMPTOMS

Field of the Invention

The present invention concerns a non-toxic oral pharmaceutical composition for use in preventing the development of hangover symptoms.

Description of Related Art

Excessive alcohol drinking typically leads to intoxication and as aftermath to hangover. Hangover is typical physically and psychically stressing syndrome and condition. The alcohol hangover is characterized by headache, tremulousness, nausea, diarrhea and fatigue combined with decreased occupational, cognitive or visual-spatial skill performance. Additionally, symptoms comprise tiredness, thirst because of dehydration, sweating and quiver. Not much is known about the pathophysiology of hangover. It is, however, known that the level of alcohol intoxication relates to the degree of hangover, not always related to the amount of alcohol intake (Ylikahri et al., 1974).

Earlier studies have shown that acetaldehyde, the first metabolite of ethyl alcohol, relates to symptoms of both intoxication and hangover (Eriksson, 2001). This concerns especially the populations of East-Asia, where acetaldehyde-induced nausea and headache symptoms have increased. (Akabane 1960; Wall et al., 2000; Yokoyama et al., 2005). Especially among these susceptible people, nausea and related vomiting usually occur already when drinking. Mainly, the high level of hangover among East-Asian people is due to lack of a specific enzyme, aldehyde dehydrogenase 2 (ALDH2), which results in failure to eliminate acetaldehyde. ALDH2-deficiency has been calculated to affect at least 540 million individuals with Eastern Asian roots, making these people at increased risk for acetaldehyde-associated carcinomas (stomach and esophagus).

These same genetic factors increasing the acetaldehyde levels appear most likely also among European populations, although not as frequent as among Asians. It follows that hangover symptoms are on an average, milder as compared to Asians (Eriksson and Fukunaga, 1993).
When considering the contribution of acetaldehyde to the unpleasant and toxic effects, such as alcohol intoxication and hangover as acute effects and tissue damage and cancer at a chronic level (Eriksson, 2001), it would be beneficial and health-promoting to find a way to reduce the levels of acetaldehyde. Concentrations of acetaldehyde in the upper digestive tract and in the stomach can be effectively reduced in connection with alcohol drinking and smoking by a very simple approach: L-cysteine capsule or lozenge (Salaspuro et al., 2002; Linderborg et al., 2011).

Hangover symptoms impair or prevent performance to work, thus leading to increased absence, raises the risk of accidents and thus reduces remarkably public health and economy. In the mid 1970's, it was estimated that in Finland, about one million working days per year are lost because of hangover (Jarvilehto et al., 1975). Today, this number is likely to be much higher. This is supported by an American study, which concludes that hangover causes $2000 average annual cost per working adult (Wiese et al., 2000). In addition, hangover typically leads to continued drinking, which in a long term increases the alcohol consumption and generates alcoholic dependency. Taken together, reducing and preventing hangover would benefit both public health and public economy.

Metabolism of alcohol takes place mainly in the liver and involves a two-step enzymatic reaction. First, alcohol is oxidized to acetaldehyde by cytoplasmic alcohol dehydrogenase (ADH) enzyme. Secondly, acetaldehyde is oxidized to acetic acid by mitochondrial and cytoplasmic aldehyde dehydrogenase (ALDH) enzymes. Acetic acid is then transported from the liver to the muscles and adipose tissue where it is further broken down into carbon dioxide and water. Thus, acetaldehyde concentrations in blood and tissues are regulated by a delicate balance between alcohols and ALDH enzymes. This is important, because although ethanol is toxic to the body, acetaldehyde is much more toxic than ethanol. Furthermore, acetaldehyde derived from alcoholic beverages has been classified as a Group 1 carcinogen for humans by the International Agency for Research on Cancer (IAIIC/WHO)/IARC 2012).

In the majority of humans, the capacity of the liver to eliminate acetaldehyde formed from ethanol is so efficient that measurable levels of acetaldehyde do not appear in the blood circulation. However, the situation is different in other tissues, e.g. in the digestive tract, where both microbes and mucosal cells can produce locally acetaldehyde from ethanol, but
are incapable of eliminating it. Therefore, in the presence of ethanol, significant amounts of acetaldehyde accumulate in the oral cavity, esophagus, stomach and large intestine (Salaspuro 2003, 2009, 2011). In fact, the highest levels of ethanol-derived acetaldehyde are found in the digestive tract.

The inventors have surprisingly found that a pharmaceutical composition eliminating or significantly reducing the amount of acetaldehyde carried to or formed in different body sites will prevent hangover symptoms, which could provide a link between hangover and alcohol consumption.

As said, the first metabolite of alcohol is acetaldehyde. The alcohol is evenly distributed in the liquid phase of the organs. Hence, after alcohol intake and as long as there is any alcohol left in the organs, the alcohol content in the blood, saliva, gastric juice and intestinal contents remain equal. Acetaldehyde is formed from the alcohol, enzymatically and by microbial action. Microbes, particularly in the digestive tract, are capable of oxidizing alcohol to acetaldehyde. Thus, even after a moderate dose of ethanol (0.5 g/kg), high acetaldehyde contents of a microbial origin (18 - 143 µM) have been measured 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 human body, acetaldehyde is formed from ethyl alcohol as a consequence of the hepatic metabolism and, locally in the digestive tract via alcohol dehydrogenase of microbial origin (Salaspuro et al, (1996) Ann Med 28:195 - 200). Saliva readily distributes from the mouth to the other areas of the upper digestive tract, whereby areas of increased exposure to acetaldehyde in the saliva include the mouth, pharynx, oesophagus and stomach. Consequently, the effects of acetaldehyde may extend to the whole upper digestive tract area.

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

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

Our recent studies have shown that all sugar (saccharose, maltose, lactose) -containing foodstuffs including beverages, can primarily contain significant amounts of acetaldehyde; 5 to 2000 µM and also ethanol, 0.1 to 0.5 ppm, or 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).

Based on recent studies, acetaldehyde seems to play an important causal role in the development of hangover symptoms. Since there are no universally effective measures to prevent hangover as yet, there is an urgent need to develop such measures.

**Summary of the Invention**

It is an aim of the present invention to provide compositions, which can be used to prevent hangover symptoms. Particularly, it is an aim of the invention to provide compositions for use in the prevention of hangovers, which compositions also 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.

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 pharmaceutical additives, which regulate the release rate of the active agents.
More specifically, the composition of the present invention is characterized by what is stated in the characterizing part of Claim 1.

Further, the method of the present invention is characterized by what is stated in Claim 16.

Considerable advantages are obtained by means of the invention. Most importantly, the present invention provides an effective composition and a method for use in preventing hangover.

The compositions are effective in releasing the active agents in the mouth or in the stomach, and binding acetaldehyde, in particular, when they are consumed in connection with eating, drinking or smoking, i.e., just before, during or immediately after eating, drinking or smoking.

These compositions can be used also in a regular basis, e.g. at 6 to 8-hour intervals. The composition comprises one or more carriers that regulate the release of the active substances, thus giving a continuous effect.

Next, the present technology will be described more closely with reference to the detailed description.

**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 compounds, combined with one or more carriers, the composition being intended for use in preventing hangover symptoms.

The term "cysteine compound" is intended to mean an amino acid 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 chemical reaction of this cysteine compound with acetaldehyde in the gastrointestinal tract.
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, preferably being L-cysteine.

According to another embodiment, one or more vitamins 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, B₁, B₂, B₃, B₆, B₉, or Bi2, due to the contents of reactive functional groups of these compounds, or a salt thereof, or any combination of the previous.

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 multi-particular 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 in 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 a granulated form.

The function of the cysteine or the N-acetyl-cysteine is based on the neutralization of acetaldehyde formed during consumption of alcohol, smoking, 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 potentially amplifying the acetaldehyde-binding effect of the cysteine compound.

The function of the diamine oxidase (i.e. histaminase) is based on its enzymatic activity in degrading histamine, whereby reducing the contribution of histamine in the development of hangover symptoms.
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 optionally 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 or other drink, or formed during the consumption of foodstuff, alcohol or other drink, or after eating, drinking or smoking, or at least keeping the acetaldehyde content essentially lower than without the use of the composition. In the case of diamine oxidase, an effective amount means an amount capable of degrading an excess of histamine present in the foodstuffs or 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 without 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 oesophagus and stomach via normal wash-out of saliva. Further, the alcohol reaching the blood circulation will be spread throughout the body and into the organs, where it can cause harm as such or when metabolized into acetaldehyde. Thus, the harm is, at least in part, systemic.

Such a harmful content of acetaldehyde in the mouth, oesophagus, stomach or intestines, and to a small extent in the other organs, can be formed as a result of consuming alcoholic drinks, particularly strong alcoholic drinks, or ingestion of foodstuffs containing alcohol or acetaldehyde, in particular among people having atrophic gastritis or an achlorhydric (acid-free) stomach.
"Alcoholic drinks" are ethanol-containing drinks, their ethanol content varying between 0.7% and 84% by volume."

"Alcoholic foodstuffs" refer to all 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-containing foodstuffs" refer to all foodstuffs containing measurable amounts of 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 flavor, or 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 particularly high concentrations 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 foodstuffs 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 intake alcoholic drinks and ends when there is no more alcohol in the blood. 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 components capable of forming alcohol or acetaldehyde in the body, 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 finishing eating.

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

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" herein refers to the local release of the cysteine compound during a time period of more than 30 minutes, preferably 0.5 to 8 hours, and most suitably in 2 to 4 hours, after administration.

According to the invention, the products formed by the binding of acetaldehyde to the active agents are inert, safe and non-toxic for the human.

In addition to cysteine and its derivatives, as well as cystine, glutathione and 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 further advantage to 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.

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

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 moistened 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 5 to 40 w-% of cysteine and 0 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 5 to 40 w-% of cysteine and 0 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.

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.

One to two 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:
Pharmaceutically acceptable diluents (fillers, extenders),
Sweeteners, such as sugars and sugar alcohols,
Flavourings, and
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, isomaltose, 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 unpleasant 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
- Cystine/glutathione/methionine
- Diluting agent(s)/sweetener(s)
- Flavouring(s)
- Lubricant(s) (0.5 to 3% by weight)

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
- Cystine/glutathione/methionine
- Gum base (comprising e.g. sweeteners)
- Flavouring
- Lubricant (0.5 to 3% by weight)
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 isomaltose.

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
- Cystine/glutathione/methionine
- Non-ionized macro molecules
- Ionizing macro molecules
- Flavouring(s)
- Lubricants
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™) and carbomer (Capropol™).

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
- Cystine/glutathione/methionine
- Diluent(s)/sweetener(s) q.s.
- Flavouring(s)
- Lubricants

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-%, and 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 the stomach. Such a composition can comprise for example:

- Cysteine
- Cystine/glutathione/methionine
- Polymer not dissolving in stomach
- Inert bulking agent
- Ethanol

The polymer not dissolving in the 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 moistened by ethanol. The moistened 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
Cystine/glutathione/methionine
Polymer not dissolving in stomach
Inert bulking agent

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
Cystine/glutathione/methionine
Water-soluble bulking agent(s)

A 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).

According to one embodiment, the composition is formulated with the help of two or more additives into a controlled-release formulation consisting of granules containing one or more active compounds, the granules being contained in a capsule, whereby at least one additive forms the capsule and at least one additive functions as a binder in the granules.

Herein the binders are selected from polymers, such as hydroxypropylmethyl cellulose, polypropylene, Carbopol or methacrylate, preferably polymers with a solution pH of 6-7, and most preferably from methacrylate derivatives, which are known by the trade names Eudragit L, Eudragit S, and Eudragit RS.

According to a further embodiment, the granules are separately coated with a polymeric film formed using porous film forming agents, such as ethyl cellulose (EC) and hydroxyl propyl methylcellulose (HPMC), preferably a mixture of these, more preferably a mixture, where the relative amount of EC to HPMC is 1/1 to 5/1, particularly 2/1 to 5/1, and most suitably 3/2 to 7/3.

According to a preferred embodiment, the composition is a non-toxic, solid and oral pharmaceutical composition for use in preventing hangover symptoms, the composition comprising one or more cysteine compounds from the group of L-cysteine, D-cysteine and N-acetyl-cysteine as active agents; optionally B12-vitamin; and one or more additives, including one or more non-toxic carriers that provide slowly controlled release of the active agents during a period of more than 30 minutes, preferably 0.5 to 8 hours and most suitably in 2 to 4 hours.

Preferably, L-cysteine is used as the active agent, Eudragit® RS-PO as a binder and CaHP0₄ as a filling agent. The active agent consists 50 to 500 mg, preferably 100 to 300 mg and most suitably about 250 mg of L-cysteine.
According to a further embodiment the composition comprises a vitamin combination consisting of Bi-, B₂-, B₆-, B₉- and Bi₂-vitamins.

According to a particularly advantageous embodiment, the composition comprises 250 mg of L-cysteine, 100 mg of Eudragit® RS-PO, 200 mg of CaHP₀₄, 73.5 mg of hydroxyl-propylmethyl-cellulose, 1.5 mg of titanium dioxide, 1.1 mg of Bi-vitamin (thiamine), 1.4 mg of B₂-vitamin (riboflavin), 16 mg of B₃-vitamin (niacin), 1.4 mg of B₆-vitamin (pyridoxine), 200 μg of Bg-vitamin (folic acid) and 2.5 μg of Bi₂-vitamin (cobalamin).

The composition comprising effective amount of cysteine 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, 5 to 40 w-% of cysteine, most suitably directly to the subject prior or in connection with the subject consuming alcohol-containing drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff.

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 prevent the development of hangover symptoms.

For example, according to an embodiment, hangover is prevented by using a method of treatment that comprises the following stages:

a) providing a subject with a composition of the present invention to be self-administered before consuming alcoholic drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff,

b) the subject self-administers the composition, and
c) the subject is allowed to drink and/or eat, and
d) optionally, the stages a) to c) are repeated as many times as feels necessary.
The method is 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.
References and related publications


Claims

1. A non-toxic, solid and oral pharmaceutical composition for use in preventing hangover symptoms, the composition comprising:
   - one or more cysteine compounds from the group of L-cysteine, D-cysteine and N-acetyl-cysteine as active agents; and
   - one or more additives, including one or more non-toxic carriers that provide slowly controlled release of the active agents during a time period of 0.5 to 8 hours after administration.

2. The composition according to claim 1 for use in preventing hangover symptoms, characterized by further comprising Bi₂-vitamin.

3. The composition according to claim 1 or 2 for use in preventing hangover symptoms, characterized by being in the form of a powder, tablet, lozenge, capsule or chewing gum.

4. The composition according to any preceding claims for use in preventing hangover symptoms, characterized by comprising L-cysteine as the active agent, methacrylate derivative such as Eudragit® RS-PO as a binder and CaHPO₄ as a filling agent.

5. The composition according to any preceding claims for use in preventing hangover symptoms, characterized in that the active agent consists of 50 to 500 mg, preferably 100 to 300 mg and most suitably about 250 mg of L-cysteine.

6. The composition according to any preceding claims for use in preventing hangover symptoms, characterized in that the composition comprises a vitamin combination consisting of Bi-, B₁₂-, B₆-, B₉- and Bi₂-vitamins.

7. The composition according to any preceding claims for use in preventing hangover symptoms, characterized in that it is formulated for slowly controlled release of the active agents in the mouth or the stomach, or for release into a food product or drink prior to consumption.
8. The composition according to any preceding claims for use in preventing hangover symptoms, 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.

9. The composition according to claim 8 for use in preventing hangover symptoms, 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.

10. The composition according to claim 8 for use in preventing hangover symptoms, characterized by selecting the non-ionized polymers from methylcellulose (MC), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG).

11. The composition according to claim 8 for use in preventing hangover symptoms, characterized by selecting the ionizing polymers from sodium carboxymethyl cellulose (NaCMC), alginic acid, sodium alginate, chitosan, polycarbofile (Noveon™) and carbomer (Capropol™).

12. The composition according to claim 8 for use in preventing hangover symptoms, characterized by selecting the diluents from lactose, calcium phosphates, starch, carboxymethyl cellulose, hydroxymethyl cellulose.

13. The composition according to any of claims 1 to 8 for use in preventing hangover symptoms, 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-%.

14. The composition according to any preceding claims for use in preventing hangover symptoms, characterized by comprising 250 mg of L-cysteine, 100 mg of Eudragit® RS-PO, 200 mg of CaHPC™4, 73.5 mg of hydroxyl-propylmethyl-cellulose, 1.5 mg of titanium dioxide, 1.1 mg of Bi-vitamin (thiamine), 1.4 mg of B2-vitamin (riboflavin), 16 mg of B3-
vitamin (niacin), 1.4 mg of B6-vitamin (pyridoxine), 200 µg of Bg-vitamin (folic acid) and 2.5 µg of Bi2-vitamin (cobalamin).

15. The composition according to any preceding claims for use in preventing hangover symptoms, characterized in that it is dosed by swallowing 1 or 2 preparations formulated from the composition at a time and repeating such action at 4 to 10-hour intervals, most preferably at 6 to 8-hour intervals.

16. A method for preventing the development of hangover symptoms, characterized by carrying out the following stages:
   a) providing a subject with a composition according to any of claims 1 to 14, to be self-administered before consuming alcoholic drinks or foodstuff, or acetaldehyde-containing drinks or foodstuff,
   b) allowing the subject to self-administer said composition, and
   c) allowing the subject to drink and/or eat,
   d) optionally, repeating the stages a) to c) as many times as feels necessary.

17. The method according to claim 16, 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.
### 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)

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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
- REGISTRY
- CAPLUS
- DWPI
- BIOSIS
- CABA
- EMBASE
- FSTA
- MEDLINE

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CN 101125170 A (KAISHENG CHENG [CN]) 20 February 2008 (20.02.2008) Tables 2 and 3 on pages 12-13 &amp; Abstract [online] EPOQUENET WPI [retrieved 10.5.2016] &amp; machine translation into English by EPO/Google [online] [retrieved 17.5.2016]: claims 1-3,6,9, examples 2 and 3</td>
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☐ 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: 27 May 2016 (27.05.2016)

Date of mailing of the international search report: 31 May 2016 (31.05.2016)

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### Box No. II  
**Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 16-17  
   because they relate to subject matter not required to be searched by this Authority, namely:  
   Claims 16-17 relate to a method or treatment of 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.
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