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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING FLAVONOIDS AND XYLITOL

(57) Abstract: The present invention relates to use of certain sugar alcohols for reduction of viruses, in particular vira causing common cold. In one embodiment, the invention relates to pharmaceutical compositions comprising a sugar alcohol, preferably xylitol. Said compositions preferably also comprise one or more flavonoids. Said composition is preferably formulated as a chewing gum. The invention also relates to treatment of common cold using said compositions.

Pharmaceutical compositions comprising flavonoids and xylitol

All patent and non-patent references cited in the application, or in the present application, are also hereby incorporated by reference in their entirety.

Field of the invention

The present invention relates to the field of chewing gums and pharmaceutical compositions comprising flavonoids. In particular, the invention relates to pharmaceutical chewing gums comprising flavonoids and xylitol. The invention furthermore relates to the use of chewing gums comprising flavonoids and xylitol as a medicament for the treatment of common cold and or similar conditions.The invention also relates to methods of treatment using said compositions, for example to methods of treating common cold and or similar conditions.

Background of the invention

Common cold is in general initiated by viral infections by the so-called cold viruses, such as rhino virus, corona virus, adenovirus, coxsackie virus, RS-virus, echovirus or other cold viruses. On average all human beings suffer 2 to 3 times a year from infections in the upper respiratory passages, such as cold and flu. In general, in Denmark the majority of common colds occurring in September, October and November are caused by rhinovirus infection, whereas the majority of common cold occurring in January, February and March are caused by Coronavirus infections. In addition, allergic syndromes may be initiated by common cold viruses, especially the rhinovirus.

Recent observations from a polymerase chain reaction (PCR)-study (Johnston, 1993) with naturally rhinovirus infected persons indicates that the actual range for rhinovirus infections involved in common cold syndrome probably is at least twofold higher, compared to findings obtained via the traditional cell culture techniques (40%). This indicates that up to 70-75% of all patients suffering from common colds

have a rhinovirus infection ongoing either as a single infection or co-infection (Spector, 1995).

It has been estimated that the average pre-school child experiences 6-10 upper respiratory infections or common colds per year whereas the average adult experiences 2-4 (Sperber, 1989). The effects of the common cold can be uncommonly disruptive, forcing otherwise normal persons to stay away from work, school, etc. Individuals who are at increased risks, such as individuals suffering from bronchitis or asthma, may also experience a life-threatening exacerbation of their underlying conditions. The average annual expenditure for various cold treatments exceeds USD 2 billion in the United States, alone (Spector, 1995); in the EU a similar figure is expected.

Unfortunately, research in development of novel strategies to treat common cold is complicated by the fact human rhinoviruses only have been reported to infect primates successfully and hence no practical animal model has been developed for rhinovirus infections (Rotbart, 2000).

The development of natural and experimentally induced rhinovirus infections in normal persons are initiated by selected events, which can be considered to occur sequentially. The steps in the rhinovirus pathogenesis are believed to include viral entry into the outer nose, mucociliary transport of virus to the posterior pharynx, and initiation of infection in ciliated and non-ciliated epithelial cells of the upper airway. Viral replication peaks on average within 48 h of initiation of infection and persists for up to 3 weeks; Infection is followed by activation of several inflammatory mechanisms, which may include release or induction of interleukins, bradykinins, prostaglandins and possibly histamine, including stimulation of parasympathetic reflexes (the cytokines may counteract each other at certain levels resulting in a very complex pathway). The resultant clinical illness is a rhinosinusitis, pharyngitis, and bronchitis, which on average lasts one week (Gwaltney, 1995).

Occasionally, a secondary bacterial or microbial infection may follow subsequently to the viral infection and a sustained and more serious inflammation may result.

Previously, it was believed that the major part of the virus was produced in the upper nose region and excreted (Winther, 1993a). However, subsequent studies, comparing recovery of virus in nasopharyngeal wash specimens, nasal swabs and pharyngeal swabs showed that the nasopharyngeal wash specimens was consistently superior to the other two specimens in yielding virus (Cate, 1964). From a series of in-depth investigations (Winther, 1984a; Winther, 1984b; Winther, 1984c; Turner, 1984; Farr, 1984; Hayden, 1987; Winther, 1987a; Winther, 1987b; Winther, 1993b; Arruda, 1995; Winther, 1998) it was concluded that:

(i) the virus was first recovered, at the highest concentrations, from the nasopharynx before it could be recovered in the upper nose region (turbinates).

(ii) no evidence for rhinovirus induced damage of the surface ciliary lining of the inferior turbinate was noted which is in agreement with other investigators suggesting that the virus may be transported to the nasopharynx in the overlaying mucus by mucociliary clearence.

(iii) there was a significant increase of the influx of neutrophils in the same area as in (ii)

(iv) infection of the lining of the nasal cavity was not uniform after intranasal inoculation and seemed not to result in any cell damage at all, cf. (ii) above.

(v) the rate of viral shedding in the nasopharynx was high by day 1 (post infection), whereas cold symptoms did not peak until day 3. The symptoms waned during the first week, but rhinovirus was present during the following 3 weeks.

(vi) The increase of neutrophils correlates with the onset of symptoms, including sore throat. The symptoms include oedema-like symptoms, which in turn may trigger sneezing and coughing.

It should be stressed that the highest concentration of virus can be recovered from the nasopharynx, and virus usually appears on the turbinate(s) one or two days later, despite the fact that virus is innoculated via the nose (in volunteers). No visible damage of the cell lining in the upper airways was ever demonstrated. Furthermore,

as "sore throat" usually develops simultaneously with the appearance of virus in the nasopharynx it can be reasoned that "signal molecules" or the like (Van Damme, 1988) will be made by the relatively few rhinovirus cells infected and that these "cytokine-like molecules" subsequently may activate the "lymphatic ring" - which is located just beneath the nasopharynx - leading to the well-known sore throat, which in turn triggers a complex pattern of inflammatory reactions, involving an array of different interferons and cytokines the interaction of which is currently under in-depth investigation. Some of these factors, such as for example Il-1, induce fever in patients. Bradykinines per se may be responsible for the sore throat, which is frequently associated with common cold.

The fact that interferon is known to be part of the non-specific innate immune response against viral infections in man has lead to several publications as a number of groups have investigated how much interferon is produced locally during viral infections of the upper-airways. One of the earliest and probably most thorough, *in vivo*, investigations in man was performed by Cate et al. (Cate, 1969) on volunteers (healthy adult males from federal correctional institutions in USA). The authors were able to demonstrate, that most of the persons involved produced interferon (as demonstrated in nasal washings) during common colds at a level, which at least theoretically should have been enough to block the viral infection, per se.

It has been demonstrated in a recent publication, that the immune system also takes “active part” in the spread of the inflammatory actions since experimental evidence supports the notion that rhinovirus may use some of the effector cells from the immune system as a mean for spreading the inflammatory reactions to the lower airways (Gern, 1996) via initiation of local TNF-alpha production. It is tempting to speculate that the allergic rhinitis is initiated via this mechanism as it has been found that the pathogenesis for asthma is linked to local TNF-alpha production (Broide et al.1992). Several quarters have thus argued that the asthma syndromes (incl. allergic rhinitis and the like) are rhinovirus manifestations of post-infectious events triggered by an array of different cytokines in connection with a “switch” between the Th1 vs. Th2 response (Gern, 1999; Winther, 1998; Grünberg, 1999).

Generally speaking, air-way infections or allergic rhinitis and/or asthma may pose serious health problems as it can be potentially life-threatening for susceptible groups in particular, such as elderly people with chronic airway problems – who often may have their normal bacterial flora changed - or persons suffering from a deficient immunity, such as AIDS-patients, cancer patients etc. Thus, simple and effective methods of treating these symptoms/syndromes and possibly also the underlying infections would be of immense importance.

Viral and/or other microbial infections are known to initiate a complex inflammatory response (Ginsburg, 1988) from the patient which probably is mediated by several groups of responder cells including the neutrophile granulocytes, which are specifically increased during a cold. The latter represents approximately more than 95% of all the effector cells. Each min. about 6-9 millions neutrophiles enter the upper-airways and slowly pass down the interior surfaces encompassing the upper airways. It may be assumed that the neutrophiles, which are able to release very aggressive enzymes and toxic substances upon proper stimulation will keep the bacterial load of the upper-airways to an acceptable level. The small numbers of S. pyogenes or S. aureus found in nasopharynx, which otherwise is almost sterile, may stimulate the neutrophiles via the so-called super-antigens to a certain degree thereby limiting the numbers of bacteria in said areas (dynamic equilibrium/symbiosis).

According to Ihrcke and co-workers (Ihrcke, 1993) the very early steps in a virus infection (or any other abnormality in the cell lining) can be related to the content and metabolism of heparan sulfate proteoglycan (the major proteoglycan associated with intact endothelial cells). The first element of the model derives from the observation that heparan sulfate is released from the intact endothelial lining of blood vessels during the very first step in an inflammatory response initiated by a viral infection. Accordingly, this loss may seriously compromise the vascular integrity and result in a local edema attracting further neutrophiles via the up-regulation of ICAM-1 markers on the endothelial cells increasing the inflammatory response further. Thus, in a separate experiment, activated neutrophiles were able to release 70% of all cell-associated heparan sulfate proteoglycan within one hour via the subsequent release of heparanase. One important function of heparan sulfate is the maintenance of the endothelial cell integrity. Loss of heparan sulfate partially

abrogates the barrier properties of the endothelium and contributes to the edema and exudation of plasma proteins that characterise inflammation.

Recently, several publications have been published claiming that the mere establishment of a viral infection in the upper as well as lower airways should be seen as a joint cooperation between the bacteria and the particular virus. For example, a few experiments have indicated that adenovirus adheres to bacteria during the penetrations processes into the target cells (host); thus, the bacteria functions as the vehicle for the virus during the early phase of infection. Along the same lines, it has been shown that the establishment of an adenovirus infection, *in vitro,* also takes place via adherences to S. pneumonia (Hakansson, Kidd et al. 1994). Furthermore, the same was also demonstrated when a non-lethal infection in mice with an influenza virus became lethal via the presence of S. pyogenes (Okamoto, Kawabata et al. 2004). Similar results were noted recently with regads to Respiratory Syncytial Virus (RSV) which was able to bind directly to S. pneumonia whereby both micro organisms became more infectious for the whole organisms (Hament, Aerts et al.).

However, no reports have published a similar effect with rhinovirus or corona virus infections in man (rhinovirus and corona virus infections are causing more than 80-90% of all common colds in man).
It has previously been attempted to treat common cold using flavonoids.

WO 02/09699 describes treatment of common cold and similar conditions, such as hayfewer using flavonoids, such as troxerutin or veneruton, either alone or in combination with metals. Flagrant used include peppermint oil.

WO 2004/037237 describes treatment of common cold and similar conditions, such as hayfewer using flavonoids, such as troxerutin or veneruton either alone or in combination with menthol.

WO 01/03681 describes treatment of viral infection, including infections related to common cold with a variety of flavonoids.

WO 01/49285 describes a medicament comprising flavonoid(s). The medicament may be useful for treatment of common cold, however this is not demonstrated.

WO 06/037319 for example describes chewing gums comprising an active ingredient and xylitol. In this application xylitol is added as a sugar-free or sugarless coating.

Summary of the invention

It is an objective of the present invention to provide new and efficient pharmaceutical compositions for treatment of common cold and similar conditions, such as rhinitis. Interestingly, the present invention surprisingly discloses that the choice of sugar and form of administration is very important.

In particular, the present invention demonstrates a surprising effect amongst sugar alcohols. A sugar alcohol is defined as a C4-C8 hydrocarbon, wherein the carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl groupInterestingly, pharmaceutical compositions comprising flavonoid and sugar alcohol such as xylitol are more efficient than similar compositions comprising other sugars in the treatment of common cold and related conditions. The administration of flavonoids and sugar alcohols such as xylitol by medical chewing gums surprisingly turned out to be even more effective than administration of flavonoids and sugar alcohols such as xylitol as lozenges.

The normal bacterial flora in the nasopharynx often contains S. pneumonia – which has been shown to be involved in many otitis media in small children (1-3 years old (Uhari, Kontiokari et al. 1998). Previously it had been shown,in vitro, that xylitol has a modest impact on the growth of this bacteria present in the nasopharynx (Kontiokari, Uhari et al. 1995). Uhari suggested using xylitol to reduce the numbers of S. pneumonia and found that xylitol was most efficacious when administered in a medical chewing gum while a lozenge was only half as effective(Uhari, Kontiokari et al. 1998). The successful treatment of otitis media was not seen with a one time treatment (a week). Rather, a successful treatment lasted for 3-4 months time (daily

intake of chewing gum with xylitol) (Tapiainen, Luotonen et al. 2002). As common cold most often is caused by viruses particularly rhinoviruses, the modest impact seen with xylitol on the specific bacteria S. pneumonia, the efficacy shown herein of xyltiol towards the symptoms of common cold was unexpected.

Recently, Turner, Fowler & Berg (2004) – cf. WO 02/09699 - demonstrated that a significant reduction in symptom score could be obtained by administering troxerutin lozenges to common cold patients in a one time treatment (3-4 days). As described above xylitol has previously been shown to have a modest impact on the growth of S. pneumonia but not on the symptoms of common cold and/or on any viruses. In order to improve the efficacy of the troxerutin lozenges it was reasoned that a one time combination treatment with troxerutin (with or without menthol) and xylitol as lozenges might be superior to treatments employing troxerutin alone (with or without menthol). The total bacteria flora – present during common cold infections - consists of a range of various bacteria including but not limited to *Corynebacterium ulcerans* including diphteriae and pyogenes, *Moraxella catarrhalis* bacteria, *Streptococcus viridans* , hemolytic streptocci, anaerobic cocci, *Hemophilus influenzae*, corynebacteria, etc, which are not known to be sensitive to xylitol. Furthermore, common cold is most often caused by viruses particularly rhinoviruses, which has not previously been shown to be sensitive to sugar alcohols, such as xylitol.

It was noted that the one time treatment (3-4 days) with the new lozenges comprising troxerutin and xylitol - turned out to be more efficacious compared to earlier treatments of common colds using lozenges with troxerutin as the only active ingredient (Turner, 2004). Surprisingly, the combination of xylitol and troxerutin gave a potentiation of the effect seen with troxerutin alone as far as reduction of the symptoms of the common cold is concerned.

However, parallel experiments conducted with chewing gums comprising troxerutin and xylitol showed that the efficacy of a medical chewing gum comprising troxerutin and xylitol and optionally menthol, far exceeded any expectations as several patients recovered in a few days time, which has not been seen previously (cf. experimental section, examples 1-6.

No previous publications or patent applications have described or suggested

the usage of combinations of flavonoids and sugar alcohols such as xylitol against common colds (including the usage of flavonoids and sugar alcohols such as xylitol against common colds or allergic rhinitis and or otitis media and or the like) in one time treatments (3-4 days). Combinations of flavonoids and sugar alcohols such as xylitol and optionally menthol were shown to be more effective than flavonoid in combination with menthol both when administered as lozenges or as chewing gums. Surprisingly administration of flavonoids and sugar alcohols such as xylitol as chewing gums turned out to be even more effective than administration of flavonoids and sugar alcohols such as xylitol as lozenges. At present, it is not known if the reason for this difference in efficacy is related with the different forms of administration. It is expected that sugar alcohols such as xylitol and anoloques thereof also might be effective in a similar ways.

Hence, it is a first objective of the present invention to provide a composition comprising one or more purified flavonoids and one or more sugar alcohols or analogues thereof for use as a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

A second objective of the invention is to provide a composition comprising one or more purified flavonoids formulated as a chewing gum for use a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

It is another obejctive of the present invention to provide a composition such as a chewing gum
comprising

i) one or more purified flavonoids
ii) one or more sugar alcohols; and
iii) menthol
iv) a gum base, and
v) optionally further pharmaceutically acceptable excipients.

It is another obejctive of the present invention to provide use of one or more purified

flavonoids and xylitols or other sugar alcohols for the preparation of a pharmaceutical composition for the treatment of a clinical condition or symptoms of a clinical condition relating to common cold in an individual in need thereof.

It is another objective of the present invention to provide methods of treatment of a clinical condition or symptoms of a clinical condition relating to common cold in an individual in need thereof, comprising administering to said individual the pharmaceutical composition or chewing gum according to the invention.

It is a further objective of the present invention to provide a medicament for treating a clinical condition comprising purified flavonoid and menthol and xylitol as active ingredients in the relevant chewing gum (or lozenges).

Preferably it is an object of the invention to provide a medicament for treating a clinical condition or symptoms of a clinical condition relating to common cold comprising purified flavonoid and sugar alcohol or an analogue thereof as active ingredients.

Another objective of the present invention to provide pharmaceutical compositions comprising

i) one or more purified flavonoids (and menthol); and
ii) xylitol; and
iii) pharmaceutically acceptable expients.
iv) a suitable chewing gum formulation the preparation of which will not damage or be detrimental for the chemical and or steric properties of troxerutin (Veneruton or other flavonoids)

Description of figures

Figure 1 illustrates the total mean symptom score of 8 common cold patients treated with Troxerutin lozenges in a similar way as described in a larger trial in 2004 (Turner, 2004); the patients were treated in a one time treatment (3-4 days) resulting in a 60% reduction in symptom score.

Figure 2 illustrates 4 patients treated in a one time treatment (3-4 days) with the new

medical chewing gum comprising xylitol and troxerutin and menthol; the recovery is significantly improved compared to the recovery mentioned above in Figure 1. Already at day 2 a 70% reduction in symptom score is noted; within 3 days treatment a significant reduction in symptom score around 90% was reached. In contrast to the above described lozenge treatment (troxerutin+xylitol+menthol) all patients responded very much the same.

Figure 3 illustrates 2 patients treated in a one time treatment (3-4 days) with the new medical chewing gum comprising xylitol and troxerutin and menthol; both patients were enrolled in the treatment before 24 h subsequent to the appearance to the usual common colds symptoms. As can be seen there is a reduction of above 75% in symptom score already after 24 h and a 100% reduction at day 2. This efficacy has not previously been reported in the litterature.

Figure 4 illustrates 3 patients treated in a one time treatment (3-4 days) with the new medical chewing gum comprising xylitol and troxerutin and menthol. These patients were enrolled in the treatment group 72 h subsequent to the appearance of the usual common cold symptoms; normally, such patients would not respond in the previos treatments with the troxerutin+menthol lozenges described in 2004 (Turner, 2004). However, during with the new treatment comprising a one time treatment (3-4 days) with medical chewing gum containing xylitol and troxerutin and menthol the patients obtained around 60% reduction in symptom score already at day 2.

Figure 5 illustrates the results from a combined study involving three groups of common cold patients treated at 48-72 hours p.i. with two different chewing gums; TroxGum (conventional chewing guma) and CompriGum (compressed chewing gum).

Detailed description

Pharmaceutical compositions and chewing gum comprising flavonoid and xylitol and optionally menthol

Surprisingly, the present invention indicates that some sugar alcohols, for example

xylitols, have an effect on the symptoms of common cold and/or an anti-bacterial effect, for example an effect on the symptoms of common cold and/or an anti-bacterial effect against a few bacteria present in nasopharynx or its surroundings (upper and or lower airways). Accordingly, in one embodiment the present invention relates to pharmaceutical compositions comprising flavonoid(s) and sugar alcohols such as xylitols as well as uses thereof. Particularly, the invention relates to one or more purified flavonoids and sugar alcohol such as xylitol or analogues thereof for use as a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

In particular the pharmaceutical compositions preferably comprises

i) one or more purified flavonoids; and
ii) purified sugars with antibacterial activitties; and
iii) pharmaceutically acceptable exipients and effective chewing gum preserving the activities of troxerutin during the manufacture process.

Preferably, the invention relates to a composition comprising

i) one or more purified flavonoids; and
ii) xylitol; and
iii) a gum base, and
iv) optionally further pharmaceutically acceptable excipients..

The purified sugar alcohol or analogue hereof may be any of the sugar alcohols or analogues described herein below.

By the term “sugar alcohol or analogue hereof” is meant a sugar alcohol, which is also known as a polyol, polyhydric alcohol, or polyalcohol. A sugar alcohol is a hydrogenated form of carbohydrate, wherein the carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group. The general formula of a sugar alcohol is $H(HCHO)_{n+1}H$, whereas the general formula of sugar is $H(HCHO)_nHCO$. In the context of the present invention is meant one or more sugar alcohols or analogues hereof essentially free of any other compounds. Hence, a composition of “sugar alcohol or analogue hereof” comprises at least 90% purified sugar alcohol or analogue hereof, preferably at least 95%

purified sugar alcohol or analogue hereof, more preferably at least 98% purified sugar alcohol or analogue hereof, even more preferably aprroximately 100% purified sugar alcohol or analogue hereof. A composition of "sugar alcohol or analogue hereof" thus most preferably does not contain any other detectable compound. In particular, it is preferred that purified purified sugar alcohol or analogue hereof are free of other compounds present in the composition from which they are purified. By way of example, if the purified sugar alcohol or analogue hereof is xylitol and is purified from a maize extract, it is preferred that the purified xylitol is essentially free of any other compounds present in the crude maize extract.

Preferably, said sugar alcohol with effect on the symptoms of common cold and/or an anti-bacterial effect is xylitol. However any other sugar alchols with effect on the symptoms of common cold and/or an anti-bacterial effect, for example analoques to xylitols or similar compounds may be used.

The flavonoid may be any of the flavonoids described herein below.

By the term "purified flavonoids" is meant one or more flavonoids essentially free of any other compounds. Hence, a composition of "purified flavonoids" comprises at least 90% flavonoid, preferably at least 95% flavonoid, more preferably at least 98% flavonoid, even more preferably aprroximately 100% flavonoid. A composition of "purified flavonoids" thus most preferably does not contain any other detectable compound. In particular, it is preferred that purified flavonoids are free of other compounds present in the composition from which they are purified. By way of example, if the flavonoid is purified from a plant extract, it is preferred that the purified flavonoids are essentially free of any other compounds present in the crude plant extract.

Preferably, the pharmaceutical compositions of the invention are essentially free of crude plant extracts or fractions thereof. The compositions may comprise fractions mainly consisting of flavonoids (menthol) or xylitols or the like.

In one embodiment of the invention, purified flavonoids and xylitol together constitutes at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80%, yet more preferably at least 90%, even more

preferably at least 95%, such as at least 98%, for example around 100% of the active ingredients of the pharmaceutical compositions of the invention.

Hence, in one preferred embodiment of the invention the pharmaceutical compositions essentially consists of

i) one or more purified flavonoids (and optionally menthol); and
ii) xylitols and
iii) pharmaceutically acceptable expients, wherein said expients are not therapeutically active such as a relevant chewing gum as previously mentioned.

By the term “essentially consists of” is meant that no other ingredients are detectable by commonly used detection techniques.

In one embodiment the composition of the invention comprises

i) one or more purified flavonoids; and
ii) one or more sugar alcohols; and
iii) a gum base, and
iv) optionally further pharmaceutically acceptable excipients.

In another embodiment the composition of the invention comprises

i) one or more purified flavonoids; and
ii) xylitol; and
iii) a gum base, and
iv) optionally further pharmaceutically acceptable excipients.

In other embodiments of the invention, the composition such as a chewing gum also comprises menthol.

The pharmaceutically acceptable excipients may for example be chewing gum carriers as defined herein below.

In this embodiment of the invention it is preferred, albeit not mandatory for the invention that purified flavonoids and sugar alcohols such as xylitol and menthol

together constitutes at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80%, yet more preferably at least 90%, even more preferably at least 95%, such as at least 98%, for example around 100% of the active ingredients of the compositions such as chewing gums of the invention.

Hence, in one preferred embodiment of the invention the pharmaceutical compositions essentially consists of

i) one or more purified flavonoids); and
ii) xylitols and
iii) pharmaceutically acceptable expients, wherein said expients are not therapeutically active such as a relevant chewing gum as previously mentioned.

In one embodiment the composition of the invention comprises

i) one or more purified flavonoids
ii) one or more sugar alcohols; and
iii) menthol, and
iv) a gum base, and
v) optionally further pharmaceutically acceptable excipients.

In another embodiment the composition of the invention comprises

i) one or more purified flavonoids; and
ii) xylitol; and
iii) menthol
iv) a gum base, and
v) optionally further pharmaceutically acceptable excipients.

In one embodiment it is preferred that the composition such as chewing gum is essentially free of other terpenes than menthol. Hence, the composition such as chewing gum is in this embodiment of the invention preferably essentially free of one or more selected from the group consisting of menthone, menthyl acetate, limonene and neomenthol. More preferably, the composition such as chewing gum is essentially free of one or more selected from the group consisting of menthone, menthyl acetate, limonene, neomenthol, piperitone, pulegone, β -caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool,

menthofurane, camphene and β-hexenyl phenylacetate. Even more preferably, the composition such as chewing gum is essentially free of menthone, menthyl acetate, limonene and neomenthol. Yet more preferably, the pharmaceutical composition is essentially free of menthone, menthyl acetate, limonene, neomenthol, piperitone, pulegone, β -caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool, menthofurane, camphene and β-hexenyl phenylacetate. It is also preferred that the composition such as chewing gum is essentially free of one or more preferably all compounds selected from the group consisting of menthone, menthyl acetate, limonene, neomenthol, piperitone, menthenone, isomenthone, pulegone, β -caryophyllene, β-caryophyllene-epoxide, α-pinene, β-pinene, germacrene D, 1,8-cineol, linalool, menthofurane, camphene and β-hexenyl phenylacetate.

In another embodiment of the invention, the compositions such as chewing gum also comprise a pharmaceutically acceptable metal complex and/or metal salt. Examples of suitable metalcomplexes and salt are given herein below.

In this embodiment of the invention it is preferred, albeit not mandatory for the invention that purified flavonoids and xylitol and metal complexes/metal salts together constitutes at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80%, yet more preferably at least 90%, even more preferably at least 95%, such as at least 98%, for example around 100% of the active ingredients of the compositions such as chewing gum of the invention.

In another preferred embodiment of the invention it is preferred, albeit not mandatory for the invention that purified flavonoids and xylitol and menthol and metal complexes and/or metal salts together constitutes at least 50%, preferably at least 60%, more preferably at least 70%, even more preferably at least 80%, yet more preferably at least 90%, even more preferably at least 95%, such as at least 98%, for example around 100% of the active ingredients of the compositions such as chewing gum of the invention.

Hence, in a very preferred embodiment of the invention the pharmaceutical

composition essentially consists of

i) one or more purified flavonoids (and optionally menthol); and
ii) xylitol; and
iii) one or more metal complexes and/or metal salts; and
iv) pharmaceutically acceptable expients, wherein said expients are not therapeutically active such as a relevant chewing gum as previously mentioned.

The term "pharmaceutical composition" should be understood in its ordinary meaning, i.e. the term does preferably not cover food, cosmetics, toothpaste and the like.

More preferably the composition such as chewing gum of the invention comprises

i) one or more purified flavonoids; and
ii) xylitol; and
iii) menthol; and
iv) one or more metal complexes and/or metal salts; and
v) a gum base, and
vi) optionally further pharmaceutically acceptable excipients.

Xylitols as a compound which may potentiate the action of an antiviral therapy

The present invention concerns efforts to diminish the influence of the bacteria flora that is present in airways and which may interact with the host in a negative fashion in that the virus attack may be enhanced. For a long time it has been known that xylitol – a natural sugar alcohol has an antibacterial effect on *Streptococcus mutant* which is present in the oral cavity as part of the normal flora, but which has a detrimental effect on the teeth via production of an enzyme that can break down the outer part of the teeth.

Xylitol has been shown by others to slow down the growth of for example, *Streptococcus pneumoniae* and other bacteria but only when used over several

months (each day). Common cold however is most often caused by viruses, particularly rhinoviruses, which have not previously been shown to be sensitive to sugar alcohols, such as xylitol. The current invention will demonstrate that although xylitol may not have a direct antibacterial effect on the normal bacterial flora, xylitol has an effect on symptoms relating to common cold and may potentiate the action of the troxerutin against common cold in a one time treatment (3-5 days) significantly which means that a new efficient method has been established for treating common cold (which is virally induced).

Preferably, said sugar alcohol with an effect on the symptoms of common cold and/or an anti-bacterial effect is xylitol. However any other sugar alchols with an effect on the symptoms of common cold and/or with anti-bacterial effects, for example analoques and derivatives of xylitols or similar compounds may be used.

Thus, the invention relates to uses of sugar alcohols such as xylitol(s) for the preparation of a composition such as a chewing gum for reduction of virus in an individual in need thereof.

Thus, the composition such as a chewing gum comprises a sugar alcohol. A sugar alcohol is defined as a C4-C8 hydrocarbon, wherein the carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group. Its general formula is $H(HCHO)_{n+1}H$, whereas sugar's is $H(HCHO)_nHCOnd$ and includes, for example, mannitol, sorbitol, inositol, galacititol, dulcitol, xylitol,ribotol, isomalt, maltitol, lactitol and arabitol. In preferred embodiments sugar alcohol is purified.

Several sugar alcohols may have similar effects as xylitol, for example, xylose, xylan, erythritol, sorbitol, glucitol, pentatioler, etc.

Preferably the sugar alcohol is selected from the group consisting of pentitols and hexitols such as xylitol, mannitol, sorbitol, galacititol (or iditol), dulcitol, ribotol (or adonitol), arabitol (or arabinitol), erythritol, or analogues thereof.

Preferably the invention relates to uses of xylitol(s) for the preparation of a composition such as a chewing gum for reduction of virus in an individual in need

thereof.

Most preferably the sugar alcohol is xylitol or an analogue thereof.

Preferably, said sugar alcohol has an effect on the symptoms of common cold and/or an anti-bacterial effect and even more preferably, said sugar alcohol with an effect on the symptoms of common cold and/or an anti-bacterial effect is xylitol. However any other sugars with an effect on the symptoms of common cold and/or an anti-bacterial effects, for example analoques and derivatives of xylitols or similar compounds may be used.

Analogues of xylitol include but are not limited to anhydrides, alkyls such as C2-C8 alkyls and -halide modifications, carbocyclic sugar mimics and bicyclic sugars of xylitol and/or synthetic analogues of xylitol.

The individual in need thereof may be any individual suffering from a condition relating to common cold. Preferably, the individual is an individual infected with one or more of the virus mentioned herein below.

The virus is preferably any of the vira described herein below in the section “Clinical conditions”. More preferably, said virus is rhinovirus.

The methods mentioned above may also be combined with administration of one or more additional active compounds. In parallel, the pharmaceutical compositions may also comprise one or more other active compounds. Said active compounds may for example be selected from the group consisting of flavonoids, metal complexes and metal salt.

The reduction of virus is preferably a reduction to at the most 80%, more preferably at the most 70%, even more preferably at the most 60%, such as at the most 50%, for example at the most 40%, such as at the most 30%, for example at the most 20%, such as at the most 10% of the initial amount of virus.

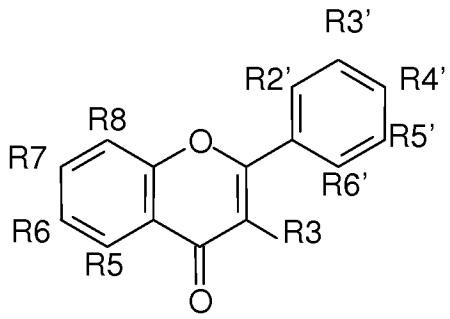
More preferably, the reduction of virus results in at least 10%, preferably at least 20%, more preferably at least 30%, for example at least 40%, such as at least 50%,

such as at least 60, for example at least 70%, such as at least 80%, for example at least 90% increase in cell survival in an in vitro test system. Cell survival may preferably be determined as for example described in Berg et al., (1999) and Berg et al. (2001).

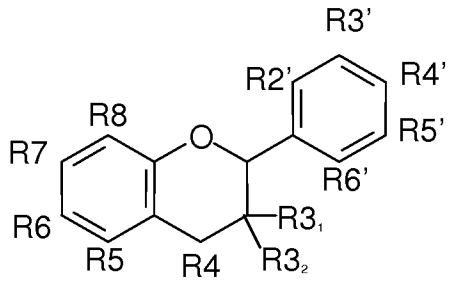
Flavonoids

"Flavonoids" useful with the present invention may be any flavonoid known to the person skilled in the art. Flavonoids are polyphenolic compounds isolated from a wide variety of plants with over 4000 individual compounds known. The term "flavonoid" according to the present invention covers both naturally occurring flavonoids as well as synthetic derivatives thereof. Flavonoids comprise a range of C_{15} aromatic compounds and are found in virtually all land-based green plants.

Preferred flavonoids according to the present invention include flavonoids of the general formula:



or the general formula:



Wherein

R2' can be selected from: -H
-OH

R3' can be selected from: -H
-OH
-OCH_3
-OCH_2CH_2OH

R4' can be selected from: -H
-OH
-OCH_3
-OCH_2CH_2OH

R5' can be selected from: -H
-OH
-OCH_3
-OCH_2CH_2OH

R6' is –H;

R3 including $R3_1$ and $R3_2$ can individually be selected from:

-H
-OH
-O-rutinose
-O-glucoside
-O-glucose-p-coumaric acid
-SOH
-O-rhamnose

R4 can be selected from:
-H
-(O)
-OH

R5 can be selected from:
-H
-OH
-O-CH_2CH_2OH

R6 can be selected from:
-H
-OH
-OCH_3

R7 can be selected from:
-H
-OH
-O-glucose
-OCH_3
-OCH_2CH_2OH
-O-glucuronic acid
-O-rutinose
-O-rhamnoglucoside

R8 can be selected from:
-H
-OH

Furthermore, flavonoid and/or flavonoid derivatives could be stereoisomers of the above mentioned. Additionally flavonoid and/or flavonoid derivatives could be dimers comprising two flavonoid subunits.

Additionally, flavonoids and/or flavonoid derivatives of the present invention to be used in combination with metal could be any flavonoid and/or flavonoid derivative known to the person skilled in the art. For example such flavonoid and/or flavonoid derivative could be any of the flavonoid and/or flavonoid derivative mentioned in WO 01/03681, which is hereby incorporated in its entirety by reference.

Preferably, the flavonoid and/or flavonoid derivatives are selected from molecules with the above general formulas with the proviso,

that when R3' is selected from	-OH $-OCH_3$ $-OCH_2CH_2OH$
then R5' is selected from	-H
and when R5' is selected from	-OH $-OCH_3$ $-OCH_2CH_2OH$
then R3' is selected from	-H

Semi-synthetic flavonoids are also within the scope of the present invention. In one embodiment of the invention the flavonoid is a synthetic flavonoid, i.e. a not naturally occurring flavonoid, such as a semi-synthetic flavonoid or a synthetic derivative of a naturally occurring flavonoid.

Preferably, the flavonoid according to the present invention could be selected from the group consisting of: troxerutin, venoruton, hydroxyethylrutosides, hesperitin, naringenin, nobiletin, tangeritin, baicalein, galangin, genistein, quercetin, apigenin, kaempferol, fisetin, rutin, luteolin, chrysin, taxifolin, eriodyctol, catecithin,

epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, flavone, sideritoflavone, hypolaetin-8-O-Gl, oroxindin, 3-hydroxyflavone, morin, quercetagetin-7-O-Gl, tambuletin, gossypin, hipifolin, naringin, leucocyanidol, amentoflavone and derivatives thereof and mixtures thereof.

More preferably, one or more of the R chains are $-OCH_2CH_2OH$, yet more preferably, at least two R chains are $-OCH_2CH_2OH$, most preferably three R chains are $-OCH_2CH_2OH$.

In one embodiment of the invention the flavonoid does not comprise antiviral activity when tested in vitro. Furthermore, it is preferred that said flavonoid is soluble in water.

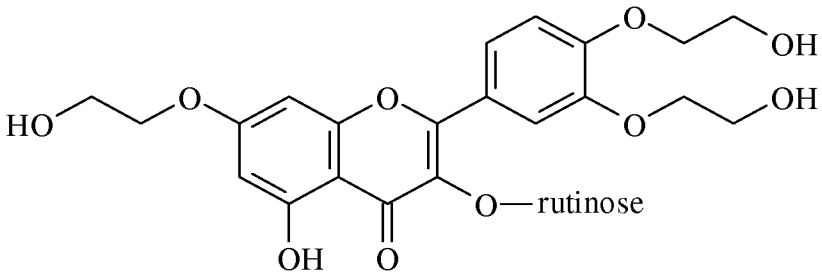
In a preferred embodiment, at least one flavonoid is a rutoside, more preferably at least one flavnoid is a hydroxyethylrutoside. Even more preferably, all the flavonoids of the composition are rutosides, yet more preferably all the flavonoids of the chewing gum or composition are hydroxyethylrutosides.

For example the chewing gum or pharmaceutical compositions of the invention may comprise a mixture of hydroxyethylrutosides, such as a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides.

In one preferred embodiment the flavonoid derivatives according to the invention comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides. More preferably, the mixture comprise 1% to 15% monohydroxyethylrutoside, such as from 5% to10% monohydroxyethylrutoside, and from 25% to 50% dihydroxyethylrutoside, such as from 30% to 38% dihydroxyethylrutoside, and from 30% to 70% trihydroxyethylrutoside, such as from 45% to 55% trihydroxyethylrutoside and from 1% to-20% tetrahydroxyethylrutoside, such as from 3% to 12% tetrahydroxyethylrutoside. Most preferably, said mixture of hydroxyethylrutosides is Venoruton.

The flavonoid is most preferably selected from the group consisting of troxerutin, Veneruton, pharmaceutical acceptable salts thereof and functional derivatives thereof.

In one especially preferred embodiment of the present invention at least one flavonoid is troxerutin of the formula:



Troxerutin

Troxerutin of the above-mentioned formula is also known as 7,3',4'-tris[O-(2-hydroxyethyl)]rutin (CAS no. 7085-55-4).

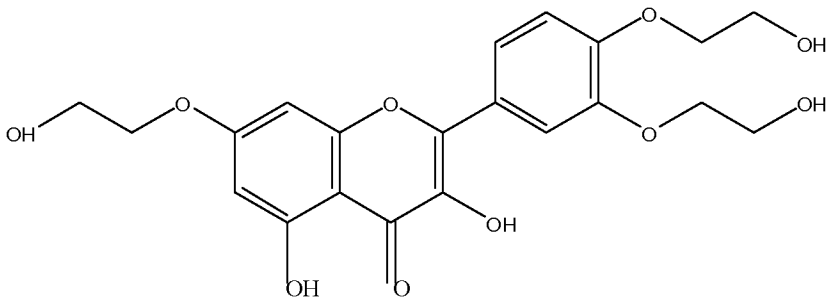
The term "Troxerutin" is in the prior art also used to designate a mixture of hydroxyethylrutosides. Hence, the pharmaceutical compositions according to the present invention may also comprise such mixtures of hydroxyethylrutosides (herein designated hydroxyethylrutoside mixture). In preferred embodiments the pharmaceutical compositions comprise no other flavonoids than a hydroxyethylrutoside mixture.

Preferably, the hydroxyethylrutoside mixture comprises at least 40%, for example around 46%, such as at least 50%, for example at least 60%, such as at least 70%, for example at least 80% troxerutin of the above-mentioned formula. The hydroxyehtylrutoside mixture may also comprise in the range of 2 to 10%, more preferably in the range of 3 to 7%, even more preferably around 5% monohydroxyehtylrutosides. The hydroxyehtylrutoside mixture may also comprise in the range of 20 to 50%, more preferably in the range of 30 to 40%, even more preferably around 34% dihydroxyehtylrutosides. The hydroxyehtylrutoside mixture may also comprise in the range of 2 to 10%, more preferably in the range of 3 to 7%, even more preferably around 5% tetrahydroxyehtylrutosides. Other hydroxyethylated components, such as hydroxyehtylated quercetin, for example tetrahydroxylated quercetin may be present in small quantities.

In one embodiment of the invention some or all of the flavonoids are aglycones. For example, at least one flavonoid may be a rutoside aglycone, preferably at least one flavonoid is a hydroxyethythyrutoside aglycone, more preferably, at least one flavonoid is troxerutin aglycone.

Aglycones are flavonoids from which at least one sugar group has been removed. Aglycones may be prepared using any suitable mechanism, for example by the aid of β-glucoronidase (see also Shimoi et al., 2001).

The chemical formula of troxerutin aglycone is shown below:



In one embodiment of the invention at least some of the flavonoids, such as essentially all flavonoids are present as metal chelates, such as chelates of iron(III), iron (II), copper(II) or zinc(II). Preferably flavonoids may be present as chelates of Zn^{2+}. Metal chelation of polyphenols is for example described in (Hider et al., 2001) and the flavonoid metalchelate may for example be formed by any of the mechanisms described therein. Preferably, the flavonoid metal chelate is Zn^{2+}/troxerutin or Zn^{2+}/Veneruton.

The pharmaceutical compositions according to the present invention may also comprise mixtures of more than one flavonoid. For example such a mixture may comprise 2, such as 3, for example 4, such as 5, for example 6, such as 7, for example 8, such as 9, for example 10, such as more than 10 different flavonoids. Preferably, such a mixture comprises 8 to 10 different flavonoids.

Menthol

In preferred embodiments the chewing gums of the present invention also comprise menthol.

The individual in need thereof may be any individual suffering from a condition relating to common cold. Preferably, the individual is an individual with a clinical condition or symptoms of a clinical condition relating to common cold or an individual infected with one or more of the vira mentioned herein below.

The virus is preferably any of the vira mentioned herein below in the section “Clinical conditions”. More preferably, said virus is rhinovirus.

The methods mentioned above may also be combined with administration of one or more other active compounds. In parallel, the pharmaceutical compositions may also comprise one or more other active compounds. Said active compounds may for example be selected from the group consisting of flavonoids, metal complexes and metal salt.

The reduction of virus is preferably a reduction to at the most 80%, more preferably at the most 70%, even more preferably at the most 60%, such as at the most 50%, for example at the most 40%, such as at the most 30%, for example at the most 20%, such as at the most 10% of the initial amount of virus.

More preferably, the reduction of virus results in at least 10%, preferably at least 20%, more preferably at least 30%, for example at least 40%, such as at least 50%, such as at least 60, for example at least 70%, such as at least 80%, for example at least 90% increase in cell survival in an in vitro test system. Cell survival may preferably be determined as for example described in Berg et al., (1999) and Berg et al., (2000).

Clinical conditions

The present invention relates to uses of flavonoids (and optionally menthol) and

sugar alcohol suc as xylitol for the preparation of a medicament for the treatment of a clinical condition. More preferably the present invention relates to one or more purified flavonoids and purified sugar alcohol such as xylitol or analogues thereof for use as a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

The invention also relates to methods of treatment of a clinical condition. The clinical condition may be any clinical condition, which may be treated using flavonoids and menthol and xylitols preferably formulated as a chewing gum. Preferably the invention also relates to a method of treatment of a clinical condition or symptoms of a clinical condition in an individual in need thereof, comprising administering to said individual the chewing gum described herein.

However, in preferred embodiments of the present invention the clinical conditions is a condition relating to common cold, such as common cold of the upper and/or lower respiratory tract and/or eyes. Conditions relating to common cold comprises common cold, a viral infection and/or a bacterial infection of the upper and/or lower respiratory tract and/or eyes, rhinitis, an allergic condition having one or more symptoms similar with the symptoms of a common cold for example allergic rhinitis initiated by rhinovirus infection, asthma like exacerbations and/or other abnormal airway functions derived from various dysfunctions of the immune system, such as for example hay fever or the like.

Furthermore, conditions relating to a common cold may comprise secondary bacterial infection(s) that follow soon after a primary viral infection. Secondary bacterial infections may for example be initiated by the normal bacterial flora present in the upper and/or lower respiratory tract and/or eyes. However, the present invention discloses that probably said infections may be down-regulated by the mere presence of sugar alcohols, such as xylitols.

Symptoms of conditions relating to common cold can be selected from the group comprising, but is not limited to: coughing, sneezing, muscle pain, sore throat, hoarseness, irritated throat, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, fever, rhinitis, swelling of mucosal membranes, pharyngitis, astma, and acute as well as chronic bronchitis.

In the present invention the upper respiratory tract includes the mouth, nose, sinuses, throat, and the respiratory tract to epiglottis. The lower respiratory tract includes the rest of the bronchial tree including the bronchioles and lung vacuoles.

The invention also relates to the treatment of eye symptoms related to the condition of the respiratory tract in that the condition may involve the mucosal lining of the respiratory tract as well of the eyes. By the term treatment as used herein is also meant prevention of symptoms whether the prevention is in fact a decrease in the development of symptoms or a prevention of the symptoms to arise in first place, e.g. upon exposure to infection.

According to the present invention a pharmaceutically effective amount or a therapeutically effective amount is to be understood as an amount sufficient to induce a desired biological result. The result can be alleviation of the signs, symptoms, or causes of a disease, for example of common cold, preferably, the result is a significant alleviation of signs, symptoms or causes of common cold. For example, an effective amount is generally that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer, preferably such a relief of symptoms is a significant relief. The relief may for example be evaluated based on a symptom score as disclosed herein in the examples. Accordingly, effective amounts can vary widely depending on the individual, on the disease or symptom to be treated.

Most common cold patients produce interferon following infection of the respiratory tract (Cate et al., 1969), which per se in principle should be sufficient to alleviate the infection.

Hence, in one preferred aspect of the present invention the treatment of a viral infection is not to be regarded as a direct antiviral effect but as a modification or inhibition of cytokines or other factors relevant for the establishment or continuation of a viral infection located in the mucosal membrane of the respiratory tract or eyes. Furthermore, the treatment preferably inhibits inflammation processes in the mucosal membrane of the respiratory tract or eyes and thereby alleviates symptoms of common cold. Accordingly, the invention relates to use of a flavonoid and xylitol

for the treatment of symptoms of viral infection of the upper and/or lower respiratory tract and/or eyes, wherein the flavonoid and/or flavonoid derivative has no antiviral effect in vitro.

Thus, in one embodiment of the present invention the flavonoid does not comprise an antiviral or anti bacterial effect in vitro. In vitro antiviral and/or antibacterial effect can be determined in various laboratory tests. Preferably, such laboratory tests comprise a cultured cell line capable of being infected with the bacteria or virus to be tested as well as said bacteria or virus. More preferably, said cultured cell line is WISH cells and said virus is a rhinovirus selected from the group consisting of: rhinovirus 1A, rhinovirus 15 and rhinovirus 39. Most preferably antiviral effect is determined using the MTS method as described in example 1. When antiviral effect is measured according to the MTS method as described in example 1, a protection of less than 10%, preferably less than 7.5%, more preferably less than 5%, even more preferably less than 3%, most preferably less than 2% is to be regarded as no antiviral effect in vitro.

Preferably, the effect of the flavonoid and/or flavonoid derivative is closely related to the living organism such as the effect is a modulatory effect on specific factors and biological reactions related to the affected mucosal membrane. The precise mechanisms are currently not known.

Very often common cold is initiated by, associated with or followed by a viral infection, which is involved in the common cold or symptoms of the common cold. In one embodiment of the present invention the condition relating to common cold is associated with a viral infection of the upper and/or lower respiratory tract and/or eyes.

The virus infection which a common cold is most often associated with or initiated by, is infection by one or more virus selected from the group consisting of: adenoviruses, parvoviruses, picornaviruses, reoviruses, orthomyxoviruses, paramyxoviruses, arenaviruses, caliciviruses, coronaviruses, orthomyxoviruses, rhinovirus, influenza virus, including influenza virus type A and B, echovirus, respiratory syncytial virus (RSV), and coxsackie virus. Rhinovirus is the most common virus identified in relation to common cold. The term rhinovirus is meant to

comprise any rhinovirus for example any of the rhinoviruses 1-113. However, very often the above virus may be present in individuals with no symptoms of common cold. Preferably, the virus infection associated with common cold according to the present invention is infection by rhinovirus or coronavirus.

Very often the common cold is associated with or followed by a bacterial infection, which is involved in the common cold or symptoms of the common cold. Such a bacterial infection may in one embodiment of the present invention be a secondary infection following a primary infection with for example a virus. In one embodiment of the present invention the condition relating to common cold is associated with a bacterial infection of the upper and/or lower respiratory tract and/or eyes.

The bacterial infection, which may be associated with a common cold or with the symptoms thereof is most often infection by one or more bacteria selected from *Streptococcus pheumoniae, Streptococcus Haemolyticae, Haemophilus influenxae,* and *Moraxella catarrhalis.* It is contemplated by the present invention that the presence and virulence of various groups of bacteria may be downregulated by sugar alcohols such as xylitol; until now this has not been demonstrated.

Furthermore, common cold may be initiated by a microbial infection. Such a microbial infection (i.e. bacterial infecttions) may lead to similar inflammatory responses as viral infections involving the same effector cells for example neutrophiles. Accordingly, such microbial infections may be treated in a fashion similar to viral infections associated with common cold.

Many allergic reactions are associated with symptoms similar to the symptoms of a common cold and it has surprisingly been shown that such symptoms of an allergic disorder may also be effectively treated by the method and use as disclosed herein. Hence, in one embodiment of the present invention the condition relating to common cold is an allergic disorder.

The allergic conditions according to the present invention are preferably selected from rhinitis, asthma, acute and chronic bronchitis, and hay fever, preferably from rhinitis and hay fever. The most common symptoms in relation to allergies are one or more symptoms selected from nasal discharge, nasal congestion, sneezing,

cough, swelling of mucosal membranes, rhinitis. More preferably, the allergic condition according to the present invention is selected from the group consisting of rhinitis and hay fever. In a further aspect of the present invention the individual may have relief from the symptoms based on a decreasing effect of said flavonoid on the mucosal swelling associated with the infection or condition mentioned herein. In a still further aspect the present invention encompass acute allergic reactions related to insect bites and sticks and in a still further aspect to the allergic reactions from food or other allergens leading to swelling of the mucosa of the mouth and/or throat in such acute reactions.

It is furthermore contained within the present invention to treat allergic conditions that is initiated by one or more agents selected from the group consisting of: pollution, house dust, common dust mite such as Dermatophagoides Farinae or Dermatophagoides Pteronyssinus, pollen such as grass pollen, tree pollen or weed pollen, mold, animal danders or feathers, fungal spores and chronic inhalation of for example, wheat flour.

Accordingly, the conditions related to common cold of the present invention could be an infection or common cold or allergic condition characterised by one or more symptoms selected from the group comprising: coughing, sneezing, muscle pain, sore throat, hoarseness, irritated throat, headache, malaise, chilliness, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis, astma, and acute as well as chronic bronchitis.

When the condition relating to common cold is an allergic condition, preferably such a condition is treated by administration of flavonoid (and optionally menthol) and a sugar alcohols such as xylitol without simultaneous administration of metal to the individual in need thereof. More preferably said flavonoid is selected from the group consisting of troxerutin and Veneruton®.

The classical common cold results in symptoms, which lasts for approximately one week. However, in certain cases conditions relating to common cold results in symptoms, which lasts for much longer. Such long lasting common colds for example last for more than 10 days, such as more than 2 weeks, such as more than 3 weeks, for example more than one month, such as more than 6 weeks. Individual

suffering from long lasting common cold are preferably treated by administration of flavonoid and menthol and xylitol without simultaneous administration of metal. More preferably said flavonoid is selected from the group consisting of troxerutin and Veneruton®.

In contrast, individuals suffering from a classical common cold wherein treatment is initiated 1 to 5 days following the onset of common cold symptoms, preferably 1 to 3 days following the onset of common cold symptoms may be treated by administration of a flavonoid, menthol, xylitol and metal according to the present invention.

Metal complexes and metal salts

In one embodiment of the invention the composition such as a chewing gum comprise flavonoid, one or more sugar alcohols such as xylitol and optionally menthol and/or a metal complex and/or metal salt.

The metal according to the present invention is preferably selected from the group consisting of zinc, manganese, cadmium, cobalt, iron and selenium. The metal may for example be in the form of Zn^{2+}, Mn^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+} and Se^{2+}. Most preferably the metal is zinc. Preferably zinc is Zn^{2+}, given in the form of a salt and/or complex or derivatives thereof.

Within the scope of the present invention, zinc could be in any suitable form for example as ZnGluconate, as $Zn(acetate)_2$, as Zn^{2+} aminochelates , as Zn^{2+} amino acid chelates, as Zn^{2+} DL-methionine, as Zn^{2+} L-methionine, as histidine derivatives or as a complex with amino acids in combination with histidine, or the like such as for example PolaPreZinc ®. Furthermore zinc could be in the form of zinc sulfate, zinc chloride, Nitric-acid zinc, phosphoric-acid zinc, ulmin acid zinc, zinc fluoride, zinc iodide, a zinc hydroxide, zinc carbonate, a zinc chromate, benzoic-acid zinc, zinc acetate, p-aminobenzoic-acid zinc, p-dimethylamino benzoic-acid zinc, p-zinc phenolsulfonate, p-methoxy cinnamic-acid zinc, lactic-acid zinc, gluconic-acid zinc, citric-acid zinc, salicylic-acid zinc, a zinc stearate, lauric-acid zinc, myristic-acid zinc, Oleic-acid zinc, 2, 5-pyridine dicarboxylic-acid zinc, 2, 6-pyridine dicarboxylic-acid zinc, 4-pyridine dicarboxylic-acid zinc, 2, 4-dicarboxy pyridine zinc, 3-hydroxy-2-

carboxy pyridine zinc, 3-n-propoxy-2-carboxy pyridine zinc, 3-n-hexyloxy-2-carboxy pyridine zinc, 5-n-propoxy-2-carboxy pyridine zinc, 5-n-butoxy-2-carboxy pyridine zinc, 5-(2-ethyl-hexyloxy)-2-carboxy pyridine zinc, 6-n-butoxy-2-carboxy pyridine zinc, 3-methoxy-2-carboxy pyridine zinc, 5-methoxy-2-carboxy pyridine zinc, 6-methoxy-2-carboxy pyridine zinc, 6-n-hexyloxy-2-carboxy pyridine zinc, 3-methyl-2-carboxy pyridine zinc, 4-methyl-2-carboxy pyridine zinc, 4-tert-butyl-2-carboxy pyridine zinc, 5-methyl-2-carboxy pyridine zinc, 5-n-hexyl-2-carboxy pyridine zinc, 3-n-undecyl-2-carboxy pyridine zinc, 4-n-undecyl-2-carboxy pyridine zinc, 5-n-butyl-2-carboxy pyridine zinc, 6-n-undecyl-2-carboxy pyridine zinc, 4-nitroglycerine-2-carboxy pyridine zinc, 5-hydroxy-2-carboxy pyridine zinc, 4-fluoro-2-carboxy pyridine zinc, 2-carboxy pyridine N-oxide zinc, picolinic-acid zinc, Nicotinic-acid zinc, nicotinamide zinc, 3, 4-dihydroxy benzoic-acid zinc, Screw histidine zinc, hinokitiol zinc, protoporphyrin zinc, porphyrin zinc or picolinic-acid amide zinc.

It is contained within the present invention that zinc could be a combination of the above mentioned zinc salts and/or a zinc complexes. Such combination could comprise two or more sorts. Preferably zinc is selected from the group consisting of Zn^{2+} aminochelates , Zn^{2+} amino acid chelates, $Zn(acetate)_2$, Zn^{2+} DL-methionine, Zn^{2+} L-methionine, ZnGluconate and PolaPreZinc ®. Preferably, zinc is in the form of ZnGluconate or PolaPreZinc®.

Administration, formulation and effect

In one aspect the present invention relates to methods of treatment involving administration of any of the chewing gums or compositions described herein above. The invention also relates to use of flavonoid(s) and sugar alcohols such as xylitol and optionally menthol for the preparation of a medicament for the treatment of a clinical condition or symptoms of a clinical condition, such as common cold. In one embodiment the invention relates to use of flavonoid and sugar alcohol, such as xylitol for the preparation of a medicament for treatment of a clinical condition, such as common cold (see herein above). The invention preferably relates to the use of one or more purified flavonoids and sugar alcohol or analogues thereof for the preparation of a medicament for the treatment of a clinical condition or symptoms of a clinical condition, wherein the clinical condition is relating to common cold.

Preferably the invention relates to one or more purified flavonoids and purified sugar alcohol or analogues thereof for use as a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

The pharmaceutical compositions according to the present invention should preferably comprise an effective dosage of flavonoids and sugar alcohol, such as xylitol and optionally of menthol and/or metal. It is contained within the present invention that the effective dosage is distributed over several dosage units. By way of example, if the pharmaceutical composition is formulated as chewing gum, then the daily effective dosage may be distributed in 1 to 50 pieces of chewing gum, such as 1 to 45 pieces of chewing gum, for example 1 to 40 pieces of chewing gum, such as 2 to 35 pieces of chewing gum, for example 2 to 30 pieces of chewing gum, preferably 2 to 25 pieces of chewing gum.

Chewing gum

The chewing gum may be produced during compressing of suitable particles which when taken by the infected person relives the active substances which must not be changed during the manufactural process. Well known methods does exist for production of various forms of medical chewing gums

In general, a chewing gum composition comprises a water soluble bulk portion, a water insoluble chewable gum base portion (also referred to as “gum base” herein), and, typically, water insoluble flavors. The water soluble portion dissipates with a portion of the flavor over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew.

The gum base portion of the chewing gum is characterized by being retained in the mouth throughout the chew. In contrast to this, some other chewing gum constituents, such as coatings or syrups, are typically swallowed by the chewer during the chewing process. Other chewing gum constituents which may be comprised in the chewing gums of the invention may for instance be coated on the gum base portion of the chewing gum (“coatings”) or contained within a cavity or hollow compartment in the gum base portion, such as can be the case with syrups, liquids, and powders. The gum base according to the present invention comprises

polymers, preferably biodegradable polymers. Such polymers include degradable polyesters, polycarbonates, poly- ester amides, polypeptides, homopolymers of amino acids such as polylysine, and proteins including derivatives hereof such as e. g. protein hydrolysates including a zein hydrolysate. Particularly useful compounds of this type include polyester polymers obtained by the polymerisation of one or more cyclic esters such as lactide, glycolide, trimethylene carbonate, 6-valerolactone, p-propiolactone and s- caprolactone. Such degradable polymers may be homopolymers or copolymers, including block-polymers. Biodegradable polymers are described in more detail herein below.

Gum phase as referred to herein below refers to all phases of the chewing gum except for the coating.

Carriers and excipients

Optionally, the chewing gum according to the invention may comprise at least one pharmaceutically acceptable carrier or excipient. It is preferred that the chewing gum comprises at least one chewing gum carrier. The term “chewing gum carrier” as used herein comprises any carrier, which may normally be comprised within a chewing gum. Chewing gum carriers may for example be any of the constituents of chewing gums described herein below. The term chewing gum carriers and chewing gum ingredients are used interchangeably herein.

In an embodiment of the invention the chewing gum contains less than about 2.0 weight percent water of the chewing gum In an embodiment of the invention the chewing gum contains from about 0.01 to about 2.0 weight percent water of the chewing gum.

In an embodiment of the invention the chewing gum contains less than 1.0 weight percent water of the chewing gum In an embodiment of the invention the chewing gum contains less than 0.75 weight percent water of the chewing gum In an embodiment of the invention the chewing gum contains less than 0.2 weight percent water of the chewing gum In an embodiment of the invention the chewing gum is substantially free of water containing sweeteners or softeners.

In an embodiment of the invention the chewing gum contains at least one low

hygroscopic softener or sweetener.

In an embodiment of the invention the chewing gum contains at least one low hygroscopic softeners or chewing gum comprises powdered erythritol.

Aqueous syrups, such as corn syrup and hydrogenated corn syrup may be used, particularly if their moisture content is reduced. This can preferably be done by co-evaporating the aqueous syrup with a plasticizer, such as glycerin or propylene glycol, to a moisture content of less than 10%. Preferred compositions include hydrogenated starch hydrolyzate solids and glycerin. Such syrups and their methods of preparation are discussed in detail in U. S. Pat. No. 4,671, 967, incorporated herein by reference.

A preferred chewing gum carrier according to the invention is a biodegradable polymer, such as any of the biodegradable polymers described herein below. Thus, in a preferred embodiment the chewing comprises a compound of Formula I or a pharmaceutically acceptable salt thereof in the form of nanoparticles and at least one biodegradable polymer. The at least one biodegradable polymer may be a polyester polymer obtained by the polymerization of one or more cyclic esters by ring-opening and where at least one of the cyclic esters are selected from the groups of glycolides, lactides, lactones, cyclic carbonates or mixtures thereof.

In an embodiment of the invention the at least one biodegradable polymer is a polyester copolymer obtained by the polymerization of two or more cyclic esters by ring-opening and where at least one of the cyclic esters are selected from the groups of glycolides, lactides, lactones, cyclic carbonates or mixtures thereof.

In an embodiment of the invention the rheological properties of the degradable polymer is controlled by adjusting the functional number of initiator.

In an embodiment of the invention the lactone monomers are chosen from the group of -caprolactone, 6-valerolactone, y-butyrolactone, andp-propiolactone. It also includes-caprolactones,8-valerolactones,y-butyrolactones, or P-propiolactones that have been substituted with one or more alkyl or aryl substituents at any non-carbonyl carbon atoms along the ring, including compounds in which two

substituents are contained on the same carbon atom and mixtures thereof.

In an embodiment of the invention the carbonate monomer is selected from the group of trimethylene carbonate,5-alkyl-1, 3-dioxan-2-one, 5,5-dialkyl-1, 3-dioxan-2-one, or 5-alkyl-5-alkyloxycarbonyl-1, 3-dioxan-2-one, ethylene carbonate, 3-ethyl-3-hydroxymethyl, propylene carbonate, trimethylolpropane monocarbonate, 4,6dimethyl-1, 3-propylene carbonate, 2,2-dimethyl trimethylene carbonate, and 1,3-dioxepan-2-one and mixtures thereof.

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is at least 150000 g/mol (Mn).

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is within the range of 105000 g/mol (Mn) to 1000000 g/mol (Mn), for example a molecular weight of Mw = 113, 900 g/mol.

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is within the range of 105000 g/mol (Mn) to 500000 g/mol (Mn).

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is within the range of 105000 g/mol (Mn) to 350000 g/mol (Mn).

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is within the range of 105000g/mol (Mn) to 250000 g/mol(Mn).

In an embodiment of the invention the molecular weight of at least one biodegradable polymer is less than 2000000 g/mol (Mn).

In an embodiment of the invention the polydispersity of at least one biodegradable polymer is within the range of 1 to 5.

In an embodiment of the invention the polydispersity of at least one biodegradable polymer is within the range of 1 to 2,5(21/2).

In an embodiment of the invention at least one biodegradable polymer constitutes at least 25% of the chewing gum polymers, preferably at least 50%.

In an embodiment of the invention all the biodegradable polymers comprised in the chewing gum constitute at least 25%, preferably at least 50% of the chewing gum polymers.

In an embodiment of the invention all the biodegradable polymers comprised in the chewing gum constitute at least 80%, preferably at least 90% of the chewing gum polymers.

In an embodiment of the invention at least one biodegradable polymer is a polyester copolymer having a molecular weight of less than 150000 g/mol results in an improved initial release in the resulting chewing gum.

In an embodiment of the invention at least one biodegradable polymer has a molecular weight of less than 125000 g/mol.

In an embodiment of the invention at least one biodegradable polymer is a biodegradable polyester copolymer having a molecular weight of less than 10000 g/mol.

In an embodiment of the invention said at least one biodegradable polymer is a biodegradable polyester copolymer having a molecular weight of less than 6000 g/mol Mn.

In an embodiment of the invention said chewing gum comprises at least two different biodegradable polymers, such as at least two different biodegradable polyester copolymers.

The difference in molecular weight between the at least two different polymers is preferably at least 1000 g/mol Mw. In an embodiment of the invention the difference

in molecular weight between the at least two different polymers is at least 10000 g/mol Mw. In an embodiment of the invention the difference in molecular weight between the at least two different polymers is at least 50000 g/mol Mw. When applying relatively significant differences in molecular weight between the applied biodegradable polymers, an increased possibility of tuning with respect to both texture and for instance chewing gum release may be obtained.

In an embodiment of the invention at least one of said at least two different biodegradable polymers comprises a biodegradable elastomer and at least one of said at least two different biodegradable polymers comprises a biodegradable plasticizer, said biodegradable plasticizer comprising at least one biodegradable polymer.

In an embodiment of the invention the molecular weight of said biodegradable plasticizer is in the range of 500-19.000 g/mol, preferably within the range of 1.500 - 9.000 g/mol Mn.

In an embodiment of the invention said at least two different biodegradable polymers have a different glass transition temperature Tg.

The chewing gum may for example comprise a biodegradable polymer having a relatively high glass transitions temperature mixed with a further biodegradable polymer featuring another glass temperature. Typically, the at least one further biodegradable polymer may be chosen by e. g. an elastomer having a relatively low glass transition temperature.

In an embodiment of the invention said at least two different biodegradable polymers have a different glass transition temperature Tg.

In an embodiment of the invention at least one of the biodegradable polymers, preferably a plasticizer, has a glass transition of at least +1°C.

In an embodiment of the invention at least one of the biodegradable polymers, preferably a plasticizer, has a glass transition of at least +10°C.

In an embodiment of the invention at least one of the biodegradable polymers, preferably a plasticizer, has a glass transition of at least +20°C.

In an embodiment of the invention at least one of the biodegradable polymers comprises a biodegradable elastomer.

In an embodiment of the invention the molecular weight of said a biodegradable elastomer range of 10000-1000000 g/mol Mw, preferably within the range of 30000 - 250000 g/mol Mn.

According to a preferred embodiment of the invention, at least one of the applied polymers has an Mw of at least 100000 g/mol.

In an embodiment of the invention at least one of the at least two different biodegradable polymers has a glass transition temperature of less than 0°C.

In an embodiment of the invention at least one of the at least two different biodegradable polymers has a glass transition temperature of less than-30°C, preferably less than -50°C In an embodiment of the invention at least two different biodegradable polymers and wherein the resulting chewing gum has at least two different glass transitions temperatures Tg.

In an embodiment of the invention the chewing gum comprises at least one biodegradable elastomer having a glass transition temperature Tg below 0°C and at least one biodegradable plasticizer having a glass transition temperature Tg exceeding 0°C.

In an embodiment of the invention at least one plasticizer comprises at biodegradable polymer obtained by polymerization of one or more cyclic esters.

In an embodiment of the invention the at least one elastomer comprises at biodegradable polymer obtained by polymerization of one or more cyclic esters.

In an embodiment of the invention the at least one elastomer comprises edible

polyesters.

In one embodiment the biodegradable polymer is a polymer polymerized from at least one trifunctional or higher functional initiator at least two different monomers forming the backbone of the polymer and at least one monomer selected from the group of carbonate monomers.

Preferably said at least two different monomers are cyclic.

In an embodiment of the invention the at least two different monomers forming the backbone of the polymer comprise at least one backbone monomer and a at least one backbone comonomer.

In an embodiment of the invention the at least one backbone comonomer imparts disorder in the backbone monomer chain.

According to the invention, it has been realized that the backbone chain comprises at least two different monomers.

In an embodiment of the invention the at least one backbone comonomer is effective to introduce amorphous regions in the backbone monomer chain.

In an embodiment of the invention the at least two different monomers forming the backbone of the polymer are selected from the group of lactone monomers.

In an embodiment of the invention the lactone monomers are chosen from the group of s-caprolactone, 6-valerolactone, y-butyrolactone, andp-propiolactone. It also includess-caprolactones, 8-valerolactones, y-butyrolactones,or (3-propiolactones that have been substituted with one or more alkyl or aryl substituents at any non-carbonyl carbon atoms along the ring, including compounds in which two substituents are contained on the same carbon atom.

Examples of the lactones described above are, but not limited to, -caprolactone, t-butyl caprolactone, zeta-enantholactone, deltavalerolactones, the monoalkyl-delta-valerolactones, e. g. the monomethyl-, monoethyl-, monohexyl-deltavalerolactones,

and the like; the nonalkyl, dialkyl, and trialkyl-epsilon-caprolactones, e. g. the monomethyl-, monoethyl-, monohexyl-, dimethyl-, di-n-propyl-, di-nhexyl-, trimethyl-, triethyl-, tri-n-epsilon-caprolactones, 5-nonyloxepan-2-one, 4,4, 6-or 4, 6,6-trimethyl-oxepan-2-one, 5-hydroxymethyloxepan-2-one, and the like; beta- lactones, e. g. , beta-propiolactone, beta-butyrolactone gamma-lactones, e. g., gammabutyrolactone or pivalolactone, dilactones, e. g. lactide, dilactides, glycolides, e. g. , tetramethyl glycolides, and the like, ketodioxanones, e. g. 1,4-dioxan-2one, 1, 5-dioxepan-2-one, and the like. The lactones can consist of the optically pure isomers or two or more optically different isomers or can consist of mixtures of isomers.

In an embodiment of the invention the at least one backbone monomer comprises caprolactone According to a preferred embodiment of the invention -caprolactone is chosen as the main monomer of the backbone, thereby ensuring that the main component of the backbone features a sufficiently low Tg.

In an embodiment of the invention the at least one backbone monomer has a Tg below -40°C, preferably less than -50°C.

In an embodiment of the invention the at least one backbone comonomer comprises 8-valerolactone.

According to a preferred embodiment of the invention 8-valerolactone forms a suitable backbone comonomer. Moreover, it has been realized that the requirements with respect to a low Tg may be somewhat relaxed, when compared to the constraints on the main backbone monomer.

In an embodiment of the invention said degradable polymer is polymerized by metal catalyzed ring-opening.

Preferably the carbonate monomer is selected from the group of trimethylene carbonate, 5-alkyl-1, 3-dioxan-2-one, 5,5-dialkyl-1, 3-dioxan-2-one, or 5-alkyl-5-alkyloxycarbonyl-1, 3-dioxan-2-one.

Examples of suitable cyclic carbonates are ethylene carbonate, 3-ethyl-3-hydroxymethyl trimethylene carbonate, propylene carbonate, trimethylene

carbonate, trimethylolpropane monocarbonate, 4,6dimethyl-1, 3-propylene carbonate, 2,2- dimethyl trimethylene carbonate, and 1,3-dioxepan-2-one and mixtures thereof.

According to the invention several differentcarboner monomers may be applied. The preferred carbonate monomer is trimethylene carbonate (TMC).

In an embodiment of the invention the at least one monomer selected from the group of carbonate monomers provides a means for introducing additional branching and/or crosslinking to the elastomeric polymer during ring-opening polymerization.

According to the invention cyclic carbonate in the monomer mixture yields precise control over the degree of branching and crosslinking in the final polymer. The mechanism by which the cyclic carbonate monomer imparts crosslinking is based upon the known tendency for metal catalysts, of which stannous octoate is a non-limiting example, to promote transesterification and transcarbonation reactions (intermolecular chain transfer to polymer) during polymerization.

In an embodiment of the invention said at least one polyol comprises a trifunctional or higher functional initiator.

Examples of advantageous multifunctional initiators are, but not limited to glycerol, trimethylolpropane, pentaerythritol, dipentaerythritol, ethoxylated or propoxylated polyamines and other molecules with multiple hydroxyl or other reactive groups and other molecules with multiple hydroxyl or other reactive groups and mixtures thereof.

According to a preferred embodiment of the invention, the preferred initiators are trimethylolpropane and pentaerythritol.

In an embodiment of the invention the degradable chewing gum polymer is polymerized from: about 20 to 80 wt % of the at least one backbone monomer, about 19.5 to 79.5 wt % of the at least one backbone comonomer, about 0.5 to 25 wt % of the at least one monomer selected from the group of carbonate monomers.

In an embodiment of the invention the degradable chewing gum polymer is moreover polymerized from: About 0.01 to 1.0 wt % of the at least one initiator In an embodiment of the invention the chewing gum properties of the polymer are adjusted by selection of a suitable order of the multifunctional initiator.

The molecular weight of lactone monomerer may preferably be within the range of 50-16000 g/mol preferably within the range of 100-3000 g/mol. The molecular weight of carbonate monomerer must be within the range 50-15000 g/mol preferably within the range of 100-2300 g/mol.

In an embodiment of the invention said chewing gum may in addition comprise chewing gum carriers which are flavoring agents.

In an embodiment of the invention said flavoring agents comprise natural and synthetic flavourings in the form of natural vegetable components, essential oils, essences, extracts, powders, including acids and other substances capable of affecting the taste profile In an embodiment of the invention said chewing gum comprises flavor in an amount of 0.01 to about 30 wt %, said percentage being based on the total weight of the chewing gum In an embodiment of the invention said chewing gum comprises flavor in an amount of 0.2 to about 4 wt %, said percentage being based on the total weight of the chewing gum In an embodiment of the invention said flavor comprises water soluble ingredients.

In an embodiment of the invention said water soluble flavor comprises acids.

In an embodiment of the invention, said flavor comprises water insoluble ingredients.

In an embodiment of the invention, said chewing gum ingredients comprising sweeteners.

In an embodiment of the invention said sweetener comprises bulk sweeteners In an embodiment of the invention the chewing gum comprises bulk sweeteners in an amount of about 5 to about 95% by weight of the chewing gum, more typically about 20 to about 80% by weight of the chewing gum.

In an embodiment of the invention the sweetener comprises high intensity sweeteners.

In an embodiment of the invention the high intensity sweeteners comprises sucralose, aspartame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones, thaumatin, monellin, sterioside, alone or in combination In an embodiment of the invention wherein the chewing gum comprises high intensity sweeteners in an amount of about 0 to about 1% by weight of the chewing gum, more typically about 0.05 to about 0.5 % by weight of the chewing gum. Sugar alcohols such as xylitol may be present in any phase of the chewing gum and may serve other purposes than being an active ingredient, for example may the sugar alcohols such as xylitol be added as a sweetener or as part of the coating.

In a preferred embodiment of the invention the sweetener is sorbitol.

In an embodiment of the invention, the chewing gum comprises at least one softener.

In an embodiment of the invention, the at least one softener comprises tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di-andtriglycerides, acetylated monoglycerides, fatty acids-such as stearic, palmitic, oleic and linoleic acids mixtures thereof.

In an embodiment of the invention the chewing gum comprises softeners in an amount of about 0 to about 18% by weight of the chewing gum, more typically about 0 to about 12 % by weight of the chewing gum.

In an embodiment of the invention, the chewing gum is substantially free of non-biodegradable polymers. In an embodiment of the invention the chewing gum comprises at least two ore more cyclic esters are selected from the groups of glycolides, lactides, lactones, cyclic carbonates or mixtures thereof.

In an embodiment of the invention the lactone monomers are chosen from the group ofs-caprolactone, 8-valerolactone,y-butyrolactone, andp-propiolactone. It also includes s-caprolactones,8-valerolactones, y-butyrolactones, orp-propiolactones that have been substituted with one or more alkyl or aryl substituents at any non-carbonyl carbon atoms along the ring, including compounds in which two substituents are contained on the same carbon atom.

In an embodiment of the invention the carbonate monomer is selected from the group of trimethylene carbonate,5-alkyl-1, 3-dioxan-2-one, 5,5-dialkyl-1, 3-dioxan-2-one, or5-alkyl-5-alkyloxycarbonyl-1, 3-dioxan-2-one, ethylene carbonate, 3-ethyl-3-hydroxymethyl, propylene carbonate, trimethylolpropane monocarbonate, 4,6dimethyl-l, 3-propylene carbonate, 2,2-dimethyl trimethylene carbonate, and 1,3-dioxepan-2-one and mixtures thereof.

In an embodiment of the invention the cyclic ester polymers and their copolymers resulting from the polymerization of cyclic ester monomers include, but are not limited to: poly (L-lactide); poly (D-lactide); poly (D, L-lactide); poly (mesolactide); poly (glycolide); poly(trimethylenecarbonate) ; poly (epsilon- caprolactone); poly (L lactide-co-D, L-lactide); poly (L-lactide-co-meso-lactide) ; poly (L-lactide co-glycolide); poly (L-lactide-co-trimethylenecarbonate); poly (L-lactide co-epsilon-caprolactone); poly (D, L-lactide-co-meso-lactide); poly (D, L lactide-co-glycolide); poly (D, L-lactide-co-trimethylenecarbonate) ; poly (D, L-lactide-co-epsilon-caprolactone); poly (meso-lactide-co glycolide); poly (meso-lactide-co-trimethylenecarbonate) ; poly (meso lactide-co-epsilon-caprolactone); poly(glycolide-cotrimethylenecarbonate) ; poly (glycolide-co-epsilon-caprolactone).

In an embodiment of the invention the chewing gum comprises filler.

A chewing gum base formulation may, if desired, include one or more fillers/texturisers including as examples, magnesium and calcium carbonate, sodium sulphate, ground limestone, silicate compounds such as magnesium and aluminium silicate, kaolin and clay, aluminium oxide, silicium oxide, talc, titanium oxide, mono-, di-and tri-calcium phosphates, cellulose polymers, such as wood, and combinations thereof.

In an embodiment of the invention the chewing gum comprises filler in an amount of about 0 to about 50% by weight of the chewing gum, more typically about 10 to about 40 % by weight of the chewing gum.

In an embodiment of the invention the chewing gum comprises at least one coloring agent.

According to an embodiment of the invention, the chewing gum may comprise color agents and whiteners such as FD & C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide and combinations thereof. Further useful chewing gum base components include antioxidants, e. g. butylated hydroxytoluene (BHT), butyl hydroxyanisol (BHA), propylgallate and tocopherols, and preservatives.

In an embodiment of the invention the chewing gum is coated with an outer coating.

In an embodiment of the invention the outer coating is a hard coating.

In an embodiment of the invention the hard coating is a coating selected from the group consisting of a sugar coating and a sugarless coating and a combination thereof.

In an embodiment of the invention the hard coating comprises 50 to 100% by weight of a polyol selected from the group consisting of sorbitol, maltitol, mannitol, xylitol, erythritol, lactitol and isomalt. Sugar alcohols such as xylitol may be present in any layer of the chewing gum and may serve other purposes than being an active ingredient, for example may the sugar alcohols such as xylitol be added as a sweetener or as part of the coating.

The active ingredients such as one or more of flavonoid, xylitol, menthol and metal complexes or metal salts may be the gum phase of the chewing gum or in the coating or sweetener phase such for example in the sorbitol phase of the chewing gum.

In an embodiment of the invention the outer coating is an edible film comprising at least one component selected from the group consisting of an edible film-forming

agent and a wax.

In an embodiment of the invention the film-forming agent is selected from the group consisting of a cellulose derivative, a modified starch, a dextrin, gelatine, shellac, gum arabic, zein, a vegetable gum, a synthetic polymer and any combination thereof.

In an embodiment of the invention the outer coating comprises at least one additive component selected from the group consisting of a binding agent, a moisture absorbing component, a film forming agent, a dispersing agent, an antisticking component, a bulking agent, a flavouring agent, a colouring agent, a pharmaceutically active component, a lipid component, a wax component, a sugar, an acid and an agent capable of accelerating the after-chewing degradation of the degradable polymer.

In an embodiment of the invention the outer coating is a soft coating.

In an embodiment of the invention the soft coating comprises a sugar free coating agent.

In an embodiment of the invention the chewing gum comprises conventional chewing gum polymers or resins.

In an embodiment of the invention the at least one biodegradable polymer comprises at least 5% of the chewing gum polymers.

In an embodiment of the invention all the biodegradable polymers comprised in the chewing gum comprises at least 25%, preferably at least 50% of the chewing gum polymers.

In an embodiment of the invention the biodegradable polymers comprised in the chewing gum comprises at least 80%, preferably at least 90% of the chewing gum polymers.

In an embodiment of the invention the chewing gum comprises said at least one

biodegradable polyester copolymer forming a plasticizer of the chewing gum and at least one non-biodegradable conventional elastomer. According to the invention, a biodegradable polymer according to the invention may form a substitute of a conventional natural or synthetic resin.

In an embodiment of the invention the chewing gum comprises the at least one biodegradable polyester copolymer forming an elastomer of the chewing gum and at least one non-biodegradable conventional natural or synthetic resin.

According to the invention, a biodegradable polymer according to the invention may form a substitute of a conventional low or high molecular weight elastomer.

In an embodiment of the invention said chewing gum comprises at least one biodegradable elastomer in the amount of about 0.5 to about 70% wt of the chewing gum, at least one biodegradable plasticizer in the amount of about 0.5 to about 70% wt of the chewing gum and at least one chewing gum ingredient chosen from the groups of softeners, sweeteners, flavoring agents, active ingredients and fillers in the amount of about 2 to about 80% wt of the chewing gum.

In an embodiment of the invention edible polyesters may be applied as a degradable chewing gum polymer.

Edible polyesters are obtained by esterification of at least one alcohol and one acid.

The edible polyester is produced by condensation polymerization reaction of at least one alcohol chosen from the group of trihydroxyl alcohol and dihydroxyl alcohol, and at least one acid chosen from the group consisting of dicarboxylic acid and tricarboxylic acid.

It is possible to use edible or food grade materials. Because the starting acids and alcohols are food grade materials the resultant polymers is edible.

Alcohols: Glycerol, propylene glycol, 1,3 butylene diol Acids: Citric acid, fumaric acid, adipic acid, malic acid,succinic acid, suberic acid, sebacic acid, dodecanedioic acid, glucaric acid, glutamic acid, glutaric, azelaic acid, tartaric acid Edible

polyesters can replace both elastomers and elastomer plasticizers and form 1-80% of the gum base.

In a preferred embodiment of the invention the chewing gum is compression chewing gums or chewing gums prepared at low temperatures below 30 ° C.

It is also contained within the present invention that flavonoids and sugar alcohol such as xylitol and optionally menthol and/or metal are formulated individually, and that the pharmaceutical composition thus comprises two individual formulations, which may be administered simultaneously or sequentially in any order. However, preferably they are administered simultaneously.

Chewing gum manufacture

Chewing gum is generally manufactured by sequentially adding the various chewing gum ingredients to any commercially available mixer known in the art. Generally, the ingredients are mixed by first melting the gum base and adding it to the running mixer. The gum base may alternatively be melted in the mixer. Color and emulsifiers can be added at this time. A softener such as glycerin can be added next along with syrup and part of the bulk portion. Further parts of the bulk portion may then be added to the mixer. The flavoring agent, pharmaceutical agent, and other optional ingredients are typically added with the final part of the bulk portion. The entire mixing process typically takes from five to fifteen minutes, although longer mixing times are sometimes required. Those skilled in the art will recognize that variations of this mixing procedure, or other mixing procedures, may be followed.

After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form such as by rolling into sheets and cutting into sticks, extruding into chunks, or casting into pellets. Pellet or ball gum is prepared as conventional chewing gum, but formed either into pellets that are pillow-shaped or into balls. The pellets/balls can then be coated or panned by conventional panning techniques to make a unique sugar-coated pellet gum. Conventional panning procedures generally apply a liquid coating to a pellet, which is then solidified, usually by drying the coating. The hard-shell coating layer is built up by successive coating and drying steps.

Conventional panning procedures generally coat with sucrose, but recent advances in panning have allowed the use of other carbohydrate materials to be used in the place of sucrose, yet still obtain a hard-shell coating. Some of these components include, but are not limited to, dextrose, maltose, xylitol, lactitol, palatinit and other new alditols or a combination thereof. These materials may be blended with panning modifiers including, but not limited to, gum arabic, maltodextrins, corn syrup, gelatin, cellulose type materials like carboxymethyl cellulose or hydroxymethyl cellulose, starch and modified starches, vegetable gums like alginates, locust bean gum, guar gum, and gum tragacanth, insoluble carbonates like calcium carbonate or magnesium carbonate, and talc. Antitack agents may also be added as panning modifiers, which allow the use of a variety of carbohydrates and sugar alcohols to be used in the development of new panned or coated gum products. Flavors may also be added with the sugar coating and with the bulk sweetener to yield unique product characteristics. Sugar alcohols such as xylitol may be present in any layer of the chewing gum and may serve other purposes than being an active ingredient. For example may the sugar alcohols such as xylitol be added as a sweetener or as part of the coating

In one embodiment of the invention the chewing gum is manufactured by the conventional production methods for chewing gums descrived above.

Compression chewing gum manufacture

In a preferred embodiment of the invention the pharmaceutical composition is medical chewing gum manufactured under conditions not detrimental to the chemical constitution of troxerutin and/or xylitol and/or menthol i.e.: low temperature; below 40-50° celcius, mild mechanical treatments, etc. as known in this field.

Another method applied may broadly be described as an initial conventional mixing of the gum base, as above described followed by a granulation of the obtained gum base mix. The obtained gum base granules may then be mixed with further chewing gum ingredients, such as sweeteners and flavor. This final granules mix may then be compressed under high pressure (typically when applying cooling) into to a chewing gum tablet.

This type of chewing gum, compressed chewing gum, has been widely used especially within a segment of medical chewing gum due to the thereto-related relatively careful way of handling the chewing gum ingredients and especially the active ingredient typically being quite vulnerable to for example high temperatures.

A chewing gum tablet of the above-described type is for example disclosed in DE 28 08 160. The disclosed chewing gum tablet is obtained by compression of a chewing granulate, and the tablet may be formed by several different layers of chewing granulates mixed.

Compressed chewing gum tablets are typically manufactured by applying pressure to an amount of powder by suitable compression means. Suitable compression means will be disclosed and explained below. The powder is then compressed into a compact coherent tablet.

The powder may for example comprise so-called primary particles or aggregated primary particles, also referred to as granules. When these are compressed, bonds are established between the particles or granules, thereby conferring a certain mechanical strength to the compressed tablet.

It should be noted that the above-introduced terms: powder, primary particles and granules may be somewhat misleading in the sense that the difference between primary particles and granules may very often be looked upon differently depending on the background of the user. Some may for instance regard a sweetener, such as sorbitol, as a primary particle in spite of the fact that sorbitol due to the typically preprocessing performed on sorbitol when delivered to the customer should rather be regarded as some sort of granule. The definition adopted in the description of this invention is that granules refer to macro-particles comprising more or less preprocessed primary particles. It should, however, be noted that this adoption of terms only relates to the description of background prior art and is not mandatory for defining the scope of the invention.

When pressure is applied to the powder raw material, the bulk volume is reduced and the amount of air is decreased. During this process energy is consumed. As the particles come into closer proximity to each other during the volume reduction

process, bonds may be established between the particles or granules. The formation of bonds is associated with a reduction in the energy of the system as energy is released.

Volume reduction takes place by various mechanisms and different types of bonds may be established between the particles or granules depending on the pressure applied and the properties of the particles or granules.

In a preferred embodiment of the invention the chewing gum is a compression chewing gum manufactured by the conventional production methods for compression chewing gums descrived above.

Over the last few years, however, the technique has rapidly improved especially with respect to development of gum base granulates intended for compression. Examples of such gum base granulate are described in the PCT/DK02/00461 and PCT/DK02/00462, hereby incorporated by reference.

Multi-modular chewing gum comprising a number of cohered chewing gum modules may form a single piece of chewing gum having a more than acceptable texture, including the initial chew, irrespective of the fact that different modules exhibits very different properties with respect to plasticity and elasticity.

Even though it should be expected that for example the elastic module (s) comprising gum base would affect the compression of the other layer (s) exhibiting very little elasticity, it has now been established that a final chewing gum tablet may in fact be made in one compression process, in one or several compression steps.

The gum base containing chewing modules according to the invention may typically be made on the basis of compressed gum base granulates.

The composition of chewing gum base formulations, which are admixed with chewing gum ingredients as defined below, can vary substantially depending on the particular product to be prepared and on the desired masticatory and other sensory characteristics of the final product. However, typical ranges (weight%) of the above gum base components are: 5 to 50% by weight elastomeric compounds, 5 to 55%

by weight elastomer plasticizers, 0 to 50% by weight filler/texturiser, 5 to 35% by weight softener and 0 to 1% by weight of miscellaneous ingredients such as antioxidants, colorants, etc.

Gum base granulates may be manufactured according to conventional methods or e. g. those described in the PCT/DK02/00461 and PCT/DK02/00462, hereby incorporated by reference.

One significant advantage of the present process is that the temperature throughout the entire operation can be kept at a relatively low level. This is an advantageous feature with regard to preserving the active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma of added flavoring components, which may be prone to deteriorationand/evaporation at higher temperatures.

According to the invention, active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma of added flavoring components may be added to the final blend prior to compression.

The active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma may be encapsulated in the chewing gum. Different methods of encapsulating active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma of added flavoring components, which may both refer to active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma of added flavoring components mixed into the gum base and active ingredients including flavonoids, sugar alcohols, such as xylitol and/or menthol and/or metal complexes and/or metal salts and optionally aroma of added flavoring components compressed into the chewing gum may e. g. include spray drying, spray cooling, film coating, coascervation, double emulsion method (extrusion technology) or prilling.

Materials to be used for the above-mentioned encapsulation methods may e. g. include Gelatine, Wheat protein, Soya protein, Sodiumcaseinate, Caseine, Gum arabic, Mod. starch,Hydrolyzed starches (maltodextrines), Alginates, Pectin, Carregeenan, Xanthan gum, Locus bean gum, Chitosan, Bees wax, Candelilla wax, Camauba wax, Hydrogenated vegetable oils, Zein and/or Sucrose.

Active ingredients including flavonoids, sugar alcohols such as xylitol and/or menthol and/or metal complexes and/or metal salts may be added to chewing gum. Preferably, these ingredients should be added subsequent to any significant heating or mixing. In other words, the active ingredients including flavonoids, xylitol and/or menthol and/or metal complexes and/or metal salts should preferably be added immediately prior to the compression of the final tablet.

Referring to the process, the adding of active ingredients including flavonoids, sugar alcohols such as xylitol and/or menthol and/or metal complexes and/or metal salts may be cautiously blended with pre-mixed gum base granulates and further desired ingredients, immediately prior to the final compression of the tablet.

When the gum base granules comprises pre-mixed active ingredients, a controlled release of active ingredients including flavonoids, sugar alcohols such as xylitol and/or menthol and/or metal complexes and/or metal salts may be obtained by means of at least a double active ingredients buffer. The first buffer comprising active ingredients blended into the final mix immediately prior to compression and the second buffer comprising active ingredients blended into the gum base prior to the blending of gum base and gum base ingredients.

In a very preferred embodiment of the invention the chewing gum is a compression chewing gum manufactured by the production methods for compression chewing gums descrived above.

The chewing gums according to the present invention may preferably be compression chewing gums further comprising any of the chewing gum constituents described herein above.

The active ingredients such as one or more of flavonoid, xylitol, menthol and metal

complexes or metal salts may be the gum phase of the chewing gum or in the coating or sweetener phase such for example in the sorbitol phase of the chewing gum.

Dose

The effective dosage of flavonoids may vary according to the individual in need thereof and to the particular clinical condition. In general, the effective will be in the range of from 5 to 5000 mg daily. More preferably, the effective dosage is in the range of from 10 mg to 4000 mg, such as in the range of from 30 mg to 3000 mg, even more preferably in the range of from 40 mg to 2000 mg daily, yet more preferably, in the range of from 50 mg to 1000 mg daily.

Furthermore, the effective dosage of said flavonoids could be a dosage equivalent of a dosage of troxerutin of from 5 mg to 5000 mg daily.

The effective dosage of Venoruton or troxerutin or a hydroxyethylrutoside mixture or a pharmaceutically acceptable salt or a functional derivative or a metal chelat thereof is normally in the range of from 5 to 5000 mg. In general the effective dosage is in the range of from 10 mg to 4000 mg, such as in the range of from 30 mg to 3000 mg, preferably in the range of from 40 mg to 2000 mg daily, more preferably, from in the range of 50 mg to 1000 mg daily, yet more preferably in the range of from 50 to 500 mg daily, most preferably in the range of from 100 to 300 mg daily for for example an adult human being.

The concentration of flavonoid per 1000 mg of chewing gum is in the range of 10 to 500 mg, such as in the range of 15 to 400 mg, for example in the range of 20 to 300 mg, such as in the range of 22 to 200mg, for example in the range of 25 to 100mg, such as in the range of 30 to 75mg, for example in the range of 35 to 50mg of troxerutin per 1000 mg total chewing gum.

The effective dosage of sugar alcohol and in particular of xylitol is depending on the individual to be treated in general in the range of 100 mg to 25.000 mg daily, such as 250 mg to 20.000 mg daily, for example 500 mg to 15.000 mg daily, such as

1000 to 12.000 mg daily, for example 2000 to 10.000 mg daily, such as 3000 to 9000 mg daily, such as 4000 to 8000 mg daily, preferably, the effective dosage of xylitol is in the range of 5.000 mg to 7.000 mg daily, for example, for an adult human being.

The effective dosage of sugar alcohol and in particular of xylitol per 1000 mg of chewing gum is in the range of 10 to 900 mg, such as in the range of 100 to 800 mg, for example in the range of 200 to 700 mg, such as in the range of 250 to 600mg, for example in the range of 300 to 550mg, such as in the range of 350 to 500mg of sugar alcohol and in particular of xylitol per 1000 mg total chewing gum.

The effective dosage of menthol is depending on the individual to be treated in general in the range of 1 mg to 200 mg daily. Preferably, the effective dosage of menthol is in the range of 5 mg to 100 mg daily, more preferably the effective dosage is in the range of 10 mg to 50 mg daily, even more preferably the effective dosage is in the range of 15 mg to 40 mg daily, yet more preferably the effective dosage is in the range of 20 mg to 35 mg daily for for example an adult human being.

The effective dosage of menthol per 1000 mg of chewing gum is in the range of 1 to 100 mg, such as in the range of 2 to 50 mg, for example in the range of 5 to 20 mg, such as in the range of 6 to 15 mg, for example in the range of 7 to 12 mg of menthol per 1000 mg total chewing gum.

The administration of flavonoids and sugar alcohol, such as xylitol and optionally menthol and/or metal salts according to the present invention is preferably a very frequent administration during the day. If xylitol and flavonoid and optionally menthol and/or metal salts and/or metal complex are formulated individually, the administration frequency may differ for flavonoid and xylitol and optionally menthol and/or metal salts, and/or metal complex respectively. Accordingly, the daily dosage may individually be administered in divided dosages of 1 to 36 individual dosages daily, preferably 2 to 24 times daily, more preferably 3 to 12 times daily, such as 5 to 8 times daily, for example around 6 times daily. Preferably, the first 2 doses are administrated simultaneously. The specific number of daily applications may be correlated to the individual way of administration and the severity of the symptom in question. The preferred treatment is a treatment where the medicament is present in

the mucosal membrane as constant as possible due to the theory that the individual factors involved in the maintenance of the symptoms are constantly produced in the affected mucosal membrane during the illness.

In one embodiment the compositions or chewing gums comprising flavonoids and sugar alcohols, such as xylitol and optionally menthol and/or metal salts and/or metal complex according to the present invention are administrated in combination with a second treatment such as in combination with an antiviral treatment including treatment against influenza such as TaMiFlu®, treatment against rhinitis such as Picovir®; or treatment with antibodies against streptococcus; or treatment with interferons (alpha, beta or gamma) and mixtures thereof. The antiviral agents include TamiFlu or other neuraminidase inhibitors or rimantadine or antibodies against RSV. The second treatment may also be a metal complex or metal salt (see herein above).

In another embodiment of the present invention the second treatment is administration of an anti-microbial agent (together with xylitol). Preferably, the anti-microbial agent is distinct and specific; however the anti-microbial agent may also be a general antibiotic. In particular, an anti-microbial agent may be administrated to treat conditions associated with bacterial infections.

The effective dosage of metal complex or metal salt depends on the particular metal complex or metal salt and the clinical condition to be treated. In general, however in the range of 0.1 mg to 1000 g metal is adminstrated daily. Preferably the metal is zinc. The effective dosage of Zinc depends upon the form of zinc component which is adminstrated. Preferably between 0.1 mg and 500 mg Zn^{2+} is administrated, such as between 0.5 mg and 250 mg, for example between 1 mg and 150 mg, such as between 5 mg and 100 mg, for example between 10 mg and 50 mg per dose. If the zinc compound is ZnGluconate, preferably between 5 mg and 1000 mg, more preferably between 10 mg and 500 mg, even more preferably between 10 mg and 100 mg, yet more preferably between 20 mg and 80 mg, even more preferably between 30 mg and 70 mg, most preferably around 50 mg ZnGluconate is administrated per dose. If the zinc compound is PolaPreZinc, preferably between 1 mg and 500 mg, more preferably between 5 mg and 250 mg, even more preferably between 10 mg and 100 mg, most preferably around 25 mg.

The effective dosage of metal complex or metal salt per 1000 mg of chewing gum is in the range of 0,5 to 80 mg, such as in the range of 1 to 70 mg, for example in the range of 1,5 to 60 mg, such as in the range of 2 to 50 mg, for example in the range of 5 to 35 mg, such as in the range of 3 to 27 mg of metal complex or metal salt per 1000 mg total chewing gum.

Thus, in preferred embodiments of the invention flavonoid comprises 2 to 10 % of the composition.

Thus, in preferred embodiments of the invention sugar alcohol or analogue thereof comprises 25 to 60 % of the composition.

Thus, in preferred embodiments of the invention the metal complex or metal salt comprises 0.2 to 10 % of the composition.

Thus, in preferred embodiments of the invention menthol comprises 0.2 to 10 % of the composition.

The administration of a flavonoid, sugar alcohol such as xylitol and and optionally menthol and/or metal salt and/or metal complex may be either simultaneously as separate or combined formulations or it may be sequential in any order.

It is preferred to present flavonoids and/or xylitol and/or menthol and/or metal salt and/or metal complex according to the present invention in the form of a pharmaceutical formulation. Accordingly, the present invention further provides pharmaceutical formulations, either as a single composition or as a kit of parts, for medicinal application, which comprises a flavonoid and xylitol as well and optionally menthol and/or a metal salt and/or metal complex according to the present invention or a pharmaceutically acceptable salts thereof, as herein defined, and a pharmaceutically acceptable exipient therefore.

The pharmaceutical formulations according to the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company,

19th edition, Easton, Pa. The phamaceutical formulation may have any form known to the person skilled in the art. For example the pharmaceutical formulation may be in the form of a solution, dispersion, emulsion, suspension, bioadhesive and non-bioadhesive gel, powder, micropheres, tablets, lozenges, chewing tablets, chewing gum including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C, pills, capsules, cachets, suppositories, dispersible granules, drops, sprays, aerosols, insufflators, inhalators, patches, a lollipop, ointment, lotion, cream, foam, implant, syrup or balm. The skilled person may select the appropriate administration form based on the common knowledge within the field of delivery systems for pharmaceuticals; it is important that a special chewing be used as this administration form, currently is the very most efficacious. In a very preferred embodiment of the invention the pharmaceutical formulation is in the form of a chewing gum including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C.

It is believed that the optimal effect is obtained by a direct topical application of the flavonoids and sugar alcohol such as xylitol and optionally menthol and/or metal salt and/or metal complex according to the present invention on the mucosal membrane in question. Accordingly, it is preferred that the administration is topical administration directly to the mucosal membrane, more preferably, to the mucosal membrane of the upper and/or lower respiratory tract and/or of the eyes, even more preferably the mucosal membrane of the oral cavity. The formulation should generally be distributed to a major part of the mucosal involved in the specific condition or symptom to be treated.Preferably the composition is formulated as a chewing gum as chewing gums turned out to be even more effective than administration of flavonoids and sugar alcohols such as xylitol as lozenges.

In a preferred embodiment of the invention the composition is useful for oral administration. Hence, it is preferred that the pharmaceutical composition is selected from the group consisting of lozenges, troches, capsules, syrups, tablets, lollipops, solutions, dispersions, suspensions, powders, micropheres, chewing tablets, chewing gums including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C, sprays and pills; it is important that a special chewing be used as this administration form, currently, is the very most efficacious. In a very preferred embodiment of the invention the pharmaceutical formulation is in

the form of a chewing gum including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C.

It is also preferred within the present invention that the pharmaceutical composition is a slow-release composition, i.e. that the release of active ingredients of the composition lasts for for example 1 min to 24 hours, such as for 1 min to 12 hours, for example from 1 min. to 6 hours, such as from 1 min to 1 hour.

The composition or chewing gum according to the present invention may comprise pharmaceutically acceptable exipients, which can be either solid or liquid. Preferably, such pharmaceutically acceptable exipients are not therapeutically active ingredient, but rather said exipients may be one or more substances which may act as diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders, preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material. Such exipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, lactose, pectin, dextrin, starch, gelatin, sucrose, magnesium carbonate, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Sugar alcohols, and in particular Xylitol is not regarded an exipient within the meaning of the present invention. Preferably, at least one pharmaceutically acceptable exicpient is Magnesium stearate, when the chewing gum is a compressed chewing gum. In addition, the pharmaceutical acceptable exipients may be colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

In powders, the excipient is preferably a finely divided solid, which is a mixture with the finely divided active components. In tablets, the active components are mixed with the exipient having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contains from one to about seventy percent of the active compound.

Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and/or glycerin and/or sucrose and/or acacia; and mouthwashes comprising the

active ingredient in a suitable liquid carrier. In one preferred embodiment the lozenges comprise sorbitol.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump. Most preferably the compounds of the present invention are formulated for oral administration as a chewing gum.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch and starch derivatives such as polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler. Most preferably the compounds of the present invention are formulated for oral administration as a chewing gum.

Surprisingly, the present invention discloses that even though common cold is usually caused by an infection of the upper and/or lower respiratory tract, it can be treated effectively by topical administration directly to the mucosal membrane of the oral cavity, in particular by administration of chewing gum. Since administration

directly to the mucosal membrane of the oral cavity is very convenient for the individual to be treated, it is a considerable advantage of the present invention that administration can be performed directly to said mucosal membrane. In addition, the present invention discloses that allergic rhinitis also can be treated by applying the compounds according to the present invention directly to the musocal membrane of the oral cavity. Accordingly, the compounds according to the present invention are preferably formulated as lozenges, chewing tablets, chewing gum including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C, drops, sprays and aerosols, which can be applied directly to the mucosal membrane of the oral cavity. Most preferably, the compounds according to the present invention are formulated as lozenges, which can be directly applied to the mucosal membrane of the oral cavity. Even more preferably the compounds of the invention is in the form of a chewing gum including compression chewing gums and chewing gums prepared at low temperatures below 30 ° C.

The individual in need of a treatment according to the invention could be any individual, however preferably, such individual is a human being. The individual will generally have a score relating to symptoms based on the score system as disclosed in Patients diary, (see examples) of at least 4 to 5, such as at least 6, preferably, at least 10, more preferably the patient would have a score of at least 15, whereas an individual with a score of 3 or less is not to be regarded as sick. Generally speaking a score around 5 to 6 or lower will allow the person to continue his/her work.

In a further aspect of the invention, the treatment results in a decrease in the severity of symptoms corresponding to a decrease of score as measured according to patient's diary herein of at least 15% within 24 hours, such as least 25 %, more preferably of at least 30 % in 24 hours from the start of the treatment. After 48 hours of treatment the scores is preferably decreased with at least 20% in 48 hours, such as with at least 30%, for example with around 40% to 60%, more preferably with at least 40%, yet more preferably with at least 50%, even more preferably with at least 60%, yet more preferably at least 70%, even more preferably at least 75% in 48 hours from the start of the treatment. 72 hours of treatment preferably results in a decrease of score as measured according to Patients Diary herein of at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least

55%, yet more preferably at least 59%, even more preferably at least 65%, yet more preferably at least 70%, even more preferably at least 80%, yet more preferably at least 85%, even more preferably at least 90% in 72 hours from the start of the treatment. However, the preferred decrease in symptom score is dependent on the condition relating to common cold to be treated, the scheme of treatment and the individual patient.

It is in particularly preferred that at least one symptom, preferably at least 2 symptoms, more preferably at least 3 symptoms selected from the group consisting of clogged nose, rhinorrhea, coughing, headache, sneezing and sore throat are essentially eliminated after 72 hours of treatment.

Flavonoids are known to possess anti-oxidative properties, and according to one further aspect, the flavonoid is a flavonoid having a singlet Oxygen Quenching measured as the rate constant of $^1O_2$ quenching K of from 10^4 to 10^9 M^{-1} s^{-1}. Preferably, the rate is 10^4 to 10^8 M^{-1} s^{-1}. The singlet oxygen quenching can be measured using a variety of solvents known to the person skilled in the art. Preferably, the solvent is selected from the group consisting of CD_3OD, a mixture of CCl_4 and CH_3OH of 1:3 and CH_3CN.

Examples

Example 1

Virus titrations

Rhinovirus 1A, rhinovirus 15 and rhinovirus 39 were titrated according to the tetrazolium salt (MTS)-method (Berg, Hansen et al. 1990) (Hansen, Nielsen et al. 1989)). WISH cells were seeded in a micro tray at 3000 cells per well and incubated at 37° C, 5% CO_2 overnight; the following morning the medium was replaced with 10-fold dilutions of either rhinovirus 1A, rhinovirus 15 or rhinovirus 39, respectively, in fresh medium and the trays were incubated 4-5 days at 33°C; a microscopical examination confirmed that the CytoPathogenic Effect (CPE) was fully developed (CPE equal to 100%). The minimal amount of virus (i.e.: the highest dilution of the

virus in question) which produced 100% destruction was used as "challenge virus" in the subsequent experiments. To quantitate the CPE in terms of % destruction, MTS (Berg and Owen, 2003) was added to all cultures and after 3 h incubation at 37° C (without CO_2) the trays were read in a scanner as previuosly described (Berg et al., 1990). Control cell cultures, that were not infected with virus, were included in the experiment; the latter gave the highest OD as these cells were not damaged; depending on the concentration of virus added to the different wells, the OD_{492} varied, accordingly: 100% CPE yielded a low OD(<0.200) ; 0% CPE corresponding to no infection at all (controls cell) gave a high OD (>1.200).

Interferon titration

Interferon titration was performed as follows (cf. Berg et al., 1990): 3.000 WISH cells were seeded in a microtray and on the following morning, the medium was replaced with 2-fold dilutions (from a 0-30 units/ml stock solution) of HuIFN-α-2b (Intron A) in fresh medium comprising 2% serum. After incubation overnight, the medium was replaced with fresh medium comprising challenge virus and incubated at 33° C, 5% CO_2 for 3-5 days and processed further as described in Berg et al., (1999) and Berg et al., (2000).

Example 2

Treatment of Common Cold Patients

In order to evaluate the new and surprising strategy findings several studies were performed in common cold patients infected naturally. The studies were undertaken essentially as described in patent application WO 02/09699, which is hereby incorporated by reference in its entirety.

The patients were treated with either lozenges containing Troxerutin, xylitol and menthol or medical chewing gums prepared by GumLink (Dandyvej, Vejle, Denmark) according to the instructions below:

Xylitol-troxerutin lozenges

50 mg Troxerutin

2-5 mg Zn Gluconate

4-5 mg (-) menthol
882 mg xylitol (variable amounts)
10 mg magnesium stearat

Three types of medical chewing gums were prepared; regular medical chewing gum with Troxerutin ("TroxGum") and two versions of medical comprimates with Troxerutin used as chewing gum ("CompriGum"). Two different versions of the medical comprimates (compressed chewing gum) were produced with troxerutin in either the gum phase or in the sorbitol phase (coating);

CompriGum: A two-layer gum piece; 80% of weight in Gum phase; 20% in sorbitol phase. Troxerutin is contained in the gum phase.

CompriGumR: A two-layer gum piece, 80% of weight in Gum phase, 20% in sorbitol phase. Troxerutin is contained in the sorbitol phase.

Ingredients	Compri Gum	Compri GumR	Troxgum	Troxgum tablet
Gum base	437	437	400	
Xylitol	481	530	479	
Sorbitol	229	179		
Aspartame	2,6	2,6	2	
Acesulfame	1,6	1,6	2	
Troxerutin	50	50	50	
Citric acid	13	13		
Menthol powder	11	11		
Menthol crystals			10	
Flavour; peach and/or lemon	40,3	40,3		
Zn gluconate	25	25	5	
Maltitol syrup			50	

Ammoniumchlorid			2	
Magnesium stearate	8,3	8,3		
Troxgum core				1000
Xylitol suspention				500*
TOTAL	1300mg	1300mg	1000mg	1500mg

Table 1: Ingredients in three types of Troxerutin contaning chewing gums.

* wherein about 95% of the suspension is xylitol

Release	Compri Gum	Compri GumR	Troxgum	Troxgum total
After 0,5 min chewing	62,4	81,2	-	-
After 1 min chewing	66,1	82,7	-	-
After 3 min chewing	85,7	94,2	-	59,4
After 6 min chewing	85,4	89,9	-	67,8
After 10 min chewing	97,7	92,7	-	89,2
After 15 min chewing	100	100	-	-

Table 2: Release in % in a chewing gum machine of Troxerutin in three Troxerutin contaning chewing gums.

In order to evaluate the effect of treatment the following Patients Diary was filled in by the patients and symptom score was calculated

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Patient's diary

This scheme should preferably be filled out in the evening. How is your current condition with regard to the symptoms below. In the scheme below, please state the strength of your symptoms today by inserting an X at the appropriate place: every

symptom should have points: 0 means that you have not had any symptoms at all; 4 means that you have had the worst symptoms available; etc. 0 = no symptoms, 1 = a minimum of symptoms; 2 = unpleasant symptoms; 3= considerably unpleasant symptoms; 4 = very unpleasant symptoms

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Symptom points	0	1	2	3	4
Cough					
Headache					
Hoarseness					
Nasal discharge					
Sneezing					
Nasal obstruction					
Sore throat					
Irritated throat					
Malaise					
Sore muscles					
Fever					

Have you had any side effects of the treatment? Yes □ No □

Specify_____

Do you also take any other medical treatment or other kinds of treatment apart from this test treatment? Yes □ No □

Specify_____

The scheme above may preferable be used for identifying persons in need of a treatment according to the invention and to compare the effect with other treatments or placebo.

A total score of 3 to 5 or less is regarded to be a normal condition.

_____

Unless otherwise stated, most of the patients included in this section have been treated at Doctor's Office within 24-30 h after the onset of the classical common cold symptoms; preferentially, patients with fewer ar allergic rhinitis or the like were excluded from these studies. Each patient was instructed to fill out the patients diary every day (day 0= 1st visit to the Doctor's Office) and to follow the mode of administration depemding on the mode of administration (either lozenge or TroxGum or CompriGum).

Lozenge administration: one lozenge was applied on or under the patient's tongue and was allowed to melt in a minimum period of 4-5 min. (no fluid or food should be taken the next 15-20 min.; the first 2 lozenges were taken in succession). If necessary, the patient took the next lozenge after 30-90 min.; a total number of 5-7 lozenges per day was equal to the maximal dose per day. The last lozenge was taken just before the patient went to bed. Treatment was in general continued for 3 to 4 days.

TroxGum and CompriGum administraion: the treatment was initiated by means of two pieces of TroxGum or CompriGum taken in succession; each piece was chewed fir 5-8 min.; after 1-2 h the next piece of Troxgum/CompriGum was taken, etc. a total of 5-7 pieces per day was used per patient in total.The last piece was taken just before the patient went to bed.

A few patients - who are not included in the enclosed figures as they reported back by telephone instead of using the Patient's Diary form - expressed a surprisingly fast recovery after the treatment with Trox-Gum already after the intake of 2-4 pieces of TroxGum. The rhinoea and the sore throat were substantially reduced. This effect has not previously been observed in patients treated with the lozenges.

To further examine quantitatively the efficacy of the treatment with TroxGum, common cold patients who all had reported to the Doctor's Office within 24-30 h subsequent to the appearance of the typical symptoms (no fewer, beginning rhinoea, sneezing, etc.) were treated for 3-4 days with TroxGum as described above.

The patients returned their diaries and the specific symptoms scores (SS) were

evaluated as shown in Figure 2-4. The treatment is most efficacious if the patients are treated 24 h post infection compared to 72 h p.i. However, it was a surprise to note that patients treated 72 h p.i. (Fig.4) did respond at all, as this was not usually seen with the lozenge treatment. Furthermore, the TroxGum treatment appeared to be far more efficient compared to the lozen treatement (cf. Figs. 1 with Figs. 2-3).

Example 3

A pilot study with 12 patients divided into two patient groups with progressive common cold was conducted. Normally these patients would have been excluded from the study due to the progressiveness of their colds as the current protocol recommanded treatment within 24 h p.i. The patients had all rather high average mean symptom score (around 30) compared to a score of 15 in patients treated 24 h p.i. (Fig.2). Surprisingly all but one patient reacted positively to the treatment (not shown).

Example 4

One patient who experienced the usual common cold symptoms (incl. a minor fever) was treated with TroxGum a few hours after the appearance of the usual symptoms defined by Turner (2004).

After the first two pieces of TroxGum the sore throat disappeared within 30 min.; coughing and rhinitis decreased substantially within 2-3 h; a total of 4 pieces were applied the first day and the treatment continued the following two days (4 pieces per day): more than 90% of the usual symptoms were absent at day 3.

Conclusion: TroxGum appears to act faster than the corresponding lozenge as this fast reduction in symptoms was not seen with the lozenge.

Example 5

A female patient who noticed the beginning of a cold was treated with TroxGum a few hours later according to the protocol on p.62. The following day the Symptom

score was reduced with 70% and within the next 20 hours she showed a 100% reduction in symptom score. Another patient experienced a similar cold treated with the same success cf .Figure 2. This fast, reduction in symptom score was not seen with lozenges in any patient.

A third patient who initiated the TroxGum tretment a few hours after the first sensation of symptoms of common cold appeared to respond very fast as most of the symptoms disappeared after 24 h treatment. The patient stopped the intake of TroxGum and noticed on the following day that the symptoms re-appeared. A second round of TroxGum did result in a second reduction in symptom score and this time the patient followed the protocol and kept the intake of TroxGum as described with excellent results. Thus, samedrug treatment can be applied with success even when the protocol has not been followed, which again support the notion that the administration form is important as the lozenge approach never has given similar results.

Figure 5 sgows the mean symptom score (running nose/sneezing/clogged nose) for 4 patients treated with TroxGum (2007, 48 h p.i.) and 4 patients treated with TroxGum (2006, 72 h. p.i.) and 5 patients treated with CompriGum (48 h p.i.).

Conclusion: The very fast reduction in symptom score seen in several patients treated at 24 h p.i. was not seen with the Xylitol, Troxerutin and menthol lozenges; the striking efficacy was only seen with the TroxGum treatement as illustrated in Fig.3.

The standard error bars of the symptom scores in Fig. 2 were reduced in a highly systematic pattern as the standard error bars decreased by each day of treatment, whichs indicates that the efficacy of the treatment is far more pronounced and predictable when administration by chewing gum is chosen. This phenomenon has not previously been described; nevertheless, it implies that the mode of administration per se, is crucial for obtaining an efficient and fast reduction in symptom score.

Example 6

3 patients with colds which were untreated for 72h, which had elevated symptom scores, were treated in a one time treatment (3-4 days) with TroxGum, 5-7 pieces per day (Fig. 4). Usually, such patients would not be enrolled into a common cold study as they are not expected to respond to any common cold treatments, per se. (Turner, 2004). However, during treatment with TroxGum comprising a one time treatment (3-4 days) around 60% reduction in symptom scores was seen already at day 2. Such a reduction in symptom scores in patients, who had colds that were left untreated for 72 h is rarely seen with the lozenges comprising troxerutin, xylitol and menthol, again supporting the above notion that the efficacy of a combination of xylitol and troxerutin administered as a medical chewing gum is unique.

A similar group of patients (72 h p.i.) with unusual high symptom scores (around 30) were treated with CompriGum for 3 days and compared to the pateinets treated withTroxGum. It appears that CompriGum is more efficacious as a steeper reduction in symptom score was noted, especially during the first 24 hours of treatment – cf. Figure 5. It should also be noted that the standard error bars decrease in size as has been previously noted in earlier experiments described in this application.

Example 7

Patients who noticed the beginning of a cold is treated with CompriGumR a few hours later according to the protocol on p.62. The following day the Symptom score is reduced with 70% and within the next 20 hours the patients experience a 100% reduction in symptom score.

Example 8

Three types of medical chewing gums are prepared; regular medical chewing gum with Troxerutin ("TroxGum") and two versions of medical comprimates with Troxerutin used as chewing gum ("CompriGum"). Two versions of the medical comprimates (compressed chewing gum) were produced;

CompriGum: A two-layer gum piece; 80% of weight in Gum phase; 20% in sorbitol

phase. Troxerutin is contained in the gum phase.

CompriGumR: A two-layer gum piece, 80% of weight in Gum phase, 20% in sorbitol phase. Troxerutin is contained in the sorbitol phase.

Ingredients	Compri Gum	Compri GumR	Troxgum	Troxgum tablet
Gum base	437	437	400	
Xylitol	481	530	479	
Sorbitol	229	179		
Aspartame	2,6	2,6	2	
Acesulfame	1,6	1,6	2	
Troxerutin	50	50	50	
Citric acid	13	13		
Menthol powder	20	20		
Menthol crystals			10	
Flavour; peach and lemon	40,3	40,3		
Zn gluconate	25	25	5	
Maltitol syrup			50	
Ammoniumchlorid			2	
Magnesium stearate	8,3	8,3		
Troxgum core				1000
Xylitol suspention				500*
TOTAL	1300mg	1300mg	1000mg	1500mg

Table 2: Ingredients in three types of Troxerutin contaning chewing gums.

In order to evaluate the effect of treatment the Patients Diary as described in Example 2 is filled in by the patients and symptom score is calculated

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Claims

1. A composition comprising one or more purified flavonoids and one or more sugar alcohols or analogues thereof for use as a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

2. A composition comprising one or more purified flavonoids formulated as a chewing gum for use a medicament in the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

3. The composition according to claim 2, which further comprises one or more sugar alcohols or analogues thereof.

4. The composition according to any of claims 1 and 3, wherein said sugar or sugar alcohol is selected from the group consisting of pentitols and hexitols such as xylitol, mannitol, sorbitol, galacititol (or iditol), dulcitol, ribotol (or adonitol), arabitol (or arabinitol), erythritol, or analogues thereof.

5. The composition according to any of claims 1 and 3-4, wherein the sugar alcohol or analogue thereof is xylitol or an analogue thereof.

6. The composition according to any of claims 1 and 3-5, which comprises
   i) one or more purified flavonoids; and
   ii) xylitol; and
   iii) a gum base, and
   iv) optionally further pharmaceutically acceptable excipients..

7. The composition according to any of claims 1 and 3-6, which further comprises menthol.

8. The composition according to any of claims 1 and 3-7, which comprises
   i) one or more purified flavonoids; and
   ii) xylitol; and
   iii) menthol; and
   iv) a gum base, and

v) optionally further pharmaceutically acceptable excipients..

9. The composition according to any of claims 1 and 3-8, which further comprises a pharmaceutically acceptable metal complex and/or metal salt.

10. The composition according to any of claims 1 and 3-9, which comprises

i) one or more purified flavonoids; and
ii) purified xylitol and
iii) menthol; and
iv) one or more metal complexes and/or metal salts; and
v) a gum base, and
vi) optionally further pharmaceutically acceptable excipients..

11. The composition according to any of claim 9 or 10, wherein said metal is zinc.

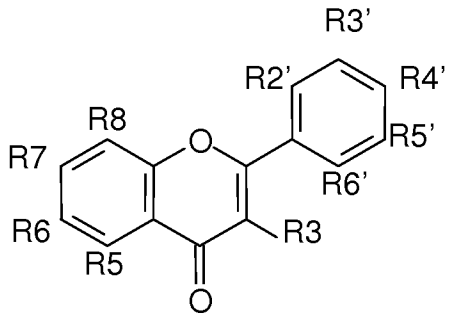
12. The composition according to any of claim 9, 10 or 11, wherein said metal is zinc selected from the group consisting of Zn^{2+} aminochelates , Zn^{2+} amino acid chelates, $Zn(acetate)_2$, Zn^{2+} DL-methionine, Zn^{2+} L-methionine, ZnGluconate and PolaPreZinc.

13. The composition according to any of claims 1 and 3-12, which is useful for oral administration.

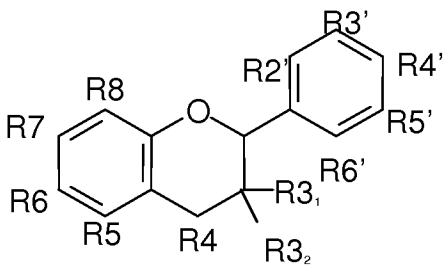
14. The chewing gum according to any of claims 1 and 3-13, wherein one or more flavonoids are chelating a metal.

15. The chewing gum according to claim 14, wherein the metal is Zn^{2+}.

16. The chewing gum according to any of claims 1 and 3-15, wherein the flavonoid is selected from the group consisting of flavonoids of the general formula:



and the general formula:



Wherein

R2' can be selected from: -H
-OH

R3' can be selected from: -H

-OH
-OCH_3
-OCH_2CH_2OH

R4' can be selected from: -H
-OH
-OCH_3
-OCH_2CH_2OH

R5' can be selected from: -H
-OH
-OCH_3
-OCH_2CH_2OH

R6' is –H;

R3 including $R3_1$ and $R3_2$ can individually be selected from:
-H
-OH
-O-rutinose
-O-glucoside
-O-glucose-p-coumaric acid
-SOH
-O-rhamnose

R4 can be selected from: -(O)
-OH

R5 can be selected from: -H
-OH
-O-CH_2CH_2OH

R6 can be selected from: -H

-OH
-OCH_3

R7 can be selected from: -H
-OH
-O-glucose
-OCH_3
-OCH_2CH_2OH
-O-glucuronic acid
-O-rutinose
-O-rhamnoglucoside

R8 can be selected from: -H
-OH

17. The composition according to any of claims 1 and 3-,16 wherein the flavonoid is selected from the group consisting of troxerutin, venoruton, hesperitin, naringenin, nobiletin, tangeritin, baicalein, galangin, genistein, quercetin, apigenin, kaempferol, fisetin, rutin, luteolin, chrysin, taxifolin, eriodyctol, catecithin, epicatechin gallate, epigallocatechin gallate, flavone, sideritoflavone, hypolaetin-8-O-Gl, oroxindin, 3-hydroxyflavone, morin, quercetagetin-7-O-Gl, tambuletin, gossypin, hipifolin, naringin, leucocyanidol, amentoflavone and derivatives thereof and mixtures thereof

18. The composition according to any of claims 1 and 3-17, wherein said flavonoid is not a naturally occurring flavonoid.

19. The composition according to any of claims 1 and 3-18, wherein said flavonoid is a rutoside.

20. The composition according to any of claims 1 and 3-19, wherein at least one flavonoid is a rutoside aglycone.

21. The composition according to any of claims 1 and 3-20, wherein said flavonoid is

a hydroxyethylrutoside.

22. The composition according to any of claims 1 and 3-21, wherein at least one flavonoid is a hydroxyethythyrutoside aglycone.

23. The composition according to any of claims 1 and 3-22, wherein said composition comprises a mixture of hydroxyethylrutosides.

24. The composition according to any of claims 1 and 3-23, wherein at least one flavonoid is troxerutin.

25. The composition according to any of claims 1 and 3-24, where at least one flavonoid is troxerutin aglycone.

26. The composition according to any of claims 1 and 3-25, wherein the flavonoid is veneruton.

27. The composition according to any of claims 1 and 3-26, wherein the at least one flavonoid is veneruton aglycone.

28. The composition according to any of claims 1 and 3-27, wherein the clinical condition is common cold of the upper and/or lower respiratory tract and/or eyes.

29. The composition according to claims 1 and 3-28, wherein the conditions relating to common cold are viral infections of the upper and/or lower respiratory tract and/or eyes.

30. The composition according to any of claims 1 and 3-29, wherein the conditions relating to common cold are bacterial infections of the upper and/or lower respiratory tract and/or eyes.

31. The composition according to any of claims 1 and 3-30, wherein the conditions relating to common cold are allergic conditions of the upper and/or lower respiratory tract and/or eyes.

32. The composition according to any of claims 1 and 3-31, wherein the conditions relating to common cold are characterized by one or more symptoms of the group comprising coughing, sneezing, muscle pain, sore throat, irritated throat, hoarseness, headache, malaise, chilliness, fever, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis, asthma, and bronchitis.

33. The composition according to claims 1 and 3-32, wherein the condition relating to common cold is a viral infection caused by or associated with one or more viruses selected from the group consisting of adenoviruses, parvoviruses, picornaviruses, reoviruses, orthomyxoviruses, paramyxoviruses, arenaviruses, caliciviruses, coronaviruses, orthomyxoviruses, rhinovirus, influenza virus, including influenza virus type A and B, echovirus and coxsackie virus.

34. The composition according to any of claims 1 and 3-33, wherein the condition relating to common cold is a viral infection caused by or associated with one or more viruses selected from the group consisting of coronaviruses and rhinoviruses.

35. The composition according to any of claims 1 and 3-34, wherein the condition relating to common cold is a bacterial infection caused by or associated with one or more bacteria selected from the group consisting of *Streptococcus pheumoniae,, Streptococcus Haemolyticae, Haemophilus influenxae,* and *Moraxella catarrhalis.*

36. The composition according to any of claims 1 and 3-35, wherein the condition relating to common cold is an allergic condition selected from the group consisting of rhinitis, acute and chronic bronchitis and hay fewer.

37. The composition according to any of claims 1 and 3-36, wherein the condition related to common cold is an allergic condition characterised by one or more symptoms selected from the group consisting of nasal discharge, nasal congestion, sneezing, cough, swelling of mucosal membranes and rhinitis.

38. The composition according to any of claims 1 and 3-37, wherein the

concentration of flavonoid is in the range of 10 to 500 mg/g, such as in the range of 15 to 400 mg/g, for example in the range of 20 to 300 mg/g, such as in the range of 22 to 200mg/g, for example in the range of 25 to 100mg/g, such as in the range of 30 to 75mg/g, for example in the range of 35 to 50mg/g of total chewing gum.

39. The composition according to any of claims 1 and 3-38, wherein the concentration of sugar alcohol and in particular of xylitol per 1000 mg of chewing gum is in the range of 10 to 900 mg/g, such as in the range of 100 to 800 mg/g, for example in the range of 200 to 700 mg/g, such as in the range of 250 to 600mg/g, for example in the range of 300 to 550mg/g, such as in the range of 350 to 500mg/g of total chewing gum.

40. The composition according to any of claims 1 and 3-39, wherein the concentration of menthol is in the range of 1 to 100 mg/g, such as in the range of 2 to 50 mg/g, for example in the range of 5 to 20 mg/g, such as in the range of 6 to 15 mg/g, for example in the range of 7 to 12 mg/g of total chewing gum.

41. The composition according to any of claims 1 and 3-40, wherein the concentration of metal complex or metal salt is in the range of 0,5 to 80 mg/g, such as in the range of 1 to 70 mg/g, for example in the range of 1,5 to 60 mg/g, such as in the range of 2 to 50 mg/g, for example in the range of 5 to 35 mg/g, such as in the range of 3 to 27 mg/g of total chewing gum.

42. The composition according to claims 1 and 3-41, wherein flavonoid comprises 2 to 10 % of the composition.

43. The composition according to any of claims 1 and 3-42, wherein the sugar alcohol or analogue thereof comprises 25 to 60 % of the composition.

44. The composition according to any of claims 1 and 3-43, wherein the metal complex or metal salt comprises 0.2 to 10 % of the composition.

45. The composition according to any of claims 1 and 3-44, wherein the menthol comprises 0.2 to 10 % of the composition.

46. The composition according to any of claims 1 and 3-45, wherein ono more of flavonoid, xylitol, menthol and metal complexes or metal salts are in the gum phase of the chewing gum.

47. The composition according to any of claims 1 and 3-46, wherein one or more of flavonoid, xylitol, menthol and metal complexes or metal salts are in the sorbitol phase of the chewing gum.

48. A chewing gum comprising

i) one or more purified flavonoids
ii) one or more sugar alcohols; and
iii) menthol; and
iv) a gum base, and
v) optionally further pharmaceutically acceptable excipients.

49. The chewing gum according to claim 48, wherein said sugar alcohol is selected from the group consisting of pentitols and hexitols such as xylitol, mannitol, sorbitol, galacititol (or iditol), dulcitol, ribotol (or adonitol), arabitol (or arabinitol), erythritol, or analogues thereof.

50. The chewing gum according to any of claims 48-49, wherein said sugar alcohol is xylitol or an analogue thereof.

51. The chewing gum according to to any of claims 48-50, which comprises

i) one or more purified flavonoids; and
ii) xylitol; and
iii) menthol, and
iv) a gum base, and
v) optionally further pharmaceutically acceptable excipients..

52. The chewing gum according to any of claims 48-51, which also comprises a pharmaceutically acceptable metal complex and/or metal salt.

53. The chewing gum according to claim 52, which comprises

i) one or more purified flavonoids; and
ii) xylitol; and
iii) menthol; and
iv) one or more metal complexes and/or metal salts; and
v) a gum base, and
vi) optionally further pharmaceutically acceptable excipients..

54. The chewing gum according to any of claims 52 or 53, wherein said metal is zinc.

55. The chewing gum according to any of claims 52 or 53 or 54, wherein the metal is zinc selected from the group consisting of Zn^{2+} aminochelates , Zn^{2+} amino acid chelates, $Zn(acetate)_2$, Zn^{2+} DL-methionine, Zn^{2+} L-methionine, ZnGluconate and PolaPreZinc ®.

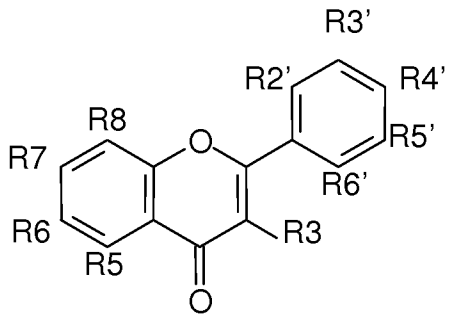
56. The chewing gum according to any of claims 48-55, wherein said chewing gum is a slow-release composition.

57. The chewing gum according to any of claims 48-56, wherein said chewing gum is compression chewing gum or chewing gum prepared at low temperatures below 30 ° C.

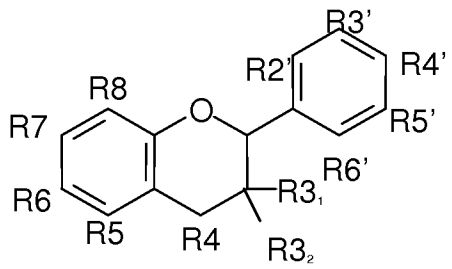
58. The chewing gum according to any of claims 48-57, wherein one or more flavonoids are chelating a metal.

59. The chewing gum according to claim 58, wherein the metal is Zn^{2+}.

60. The chewing gum according to any of claims 48-59, wherein the flavonoid is selected from the group consisting of flavonoids of the general formula:


R3'
R2'
R4'
R8
R5'
R7
O
R6'
R6
R3
R5
O

and the general formula:



Wherein

R2' can be selected from: -H
-OH

R3' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R4' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R5' can be selected from: -H
-OH
$-OCH_3$
$-OCH_2CH_2OH$

R6' is –H;

R3 including $R3_1$ and $R3_2$ can individually be selected from:

-H
-OH
-O-rutinose
-O-glucoside
-O-glucose-p-coumaric acid
-SOH
-O-rhamnose

R4 can be selected from:
-(O)
-OH

R5 can be selected from: -H
-OH
-O-CH_2CH_2OH

R6 can be selected from: -H
-OH
-OCH_3

R7 can be selected from: -H
-OH
-O-glucose
-OCH_3
-OCH_2CH_2OH
-O-glucuronic acid
-O-rutinose
-O-rhamnoglucoside

R8 can be selected from:
-H
-OH

61. The chewing gum according to any of claims 48-60, wherein the flavonoid is selected from the group consisting of troxerutin, venoruton, hesperitin, naringenin, nobiletin, tangeritin, baicalein, galangin, genistein, quercetin,

apigenin, kaempferol, fisetin, rutin, luteolin, chrysin, taxifolin, eriodyctol, catecithin, epicatechin gallate, epigallocatechin gallate, flavone, sideritoflavone, hypolaetin-8-O-Gl, oroxindin, 3-hydroxyflavone, morin, quercetagetin-7-O-Gl, tambuletin, gossypin, hipifolin, naringin, leucocyanidol, amentoflavone and derivatives thereof and mixtures thereof

62. The chewing gum according to any of claims 48-61, wherein said flavonoid is not a naturally occurring flavonoid.

63. The chewing gum according to any of claims 48-62, wherein said flavonoid is a rutoside.

64. The chewing gum according to any of claims 48-63, wherein at least one flavonoid is a rutoside aglycone.

65. The chewing gum according to any of claims 48-64, wherein said flavonoid is a hydroxyethylrutoside.

66. The chewing gum according to any of claims 48-65, wherein at least one flavonoid is a hydroxyethythyrutoside aglycone.

67. The chewing gum according to any of claims 48-66, wherein said chewing gum comprises a mixture of hydroxyethylrutosides.

68. The chewing gum according to any of claims 48-67, wherein said chewing gum comprises a mixture of mono-, di-, tri- and tetrahydroxyethylrutosides.

69. The chewing gum according to any of claims 48-68, wherein at least one flavonoid is troxerutin.

70. The chewing gum according to any of claims 48-69, where at least one flavonoid is troxerutin aglycone.

71. The chewing gum according to any of claims 48-70, wherein the flavonoid is veneruton.

72. The chewing gum according to any of claims 48-71, wherein the concentration of flavonoid is in the range of 10 to 500 mg/g, such as in the range of 15 to 400 mg/g, for example in the range of 20 to 300 mg/g, such as in the range of 22 to 200mg/g, for example in the range of 25 to 100mg/g, such as in the range of 30 to 75mg/g, for example in the range of 35 to 50mg/g of total chewing gum.

73. The chewing gum according to any of claims 48-72, wherein the concentration of sugar alcohol and in particular of xylitol per 1000 mg of chewing gum is in the range of 10 to 900 mg/g, such as in the range of 100 to 800 mg/g, for example in the range of 200 to 700 mg/g, such as in the range of 250 to 600mg/g, for example in the range of 300 to 550mg/g, such as in the range of 350 to 500mg/g of total chewing gum.

74. The chewing gum according to any of claims 48-73, wherein the concentration of menthol is in the range of 1 to 50 mg/g, such as in the range of 2 to 25 mg/g, for example in the range of 3 to 20 mg/g, such as in the range of 4 to 15 mg/g, for example in the range of 5 to 14 mg/g, such as in the range of 7 to 12 mg/g of total chewing gum.

75. The chewing gum according to any of claims 48-74, wherein the concentration of metal complex or metal salt is in the range of 0,5 to 80 mg/g, such as in the range of 1 to 70 mg/g, for example in the range of 1,5 to 60 mg/g, such as in the range of 2 to 50 mg/g, for example in the range of 5 to 35 mg/g, such as in the range of 3 to 27 mg/g of total chewing gum.

76. The chewing gum according to any of claims 48-75, wherein flavonoid comprises 2 to 10 % of the composition.

77. The chewing gum according to any of claims 48-76, wherein the sugar alcohol or analogue thereof comprises 25 to 60 % of the composition.

78. The chewing gum according to any of claims 48-77, wherein the metal complex or metal salt comprises 0.2 to 10 % of the composition.

79. The chewing gum according to any of claims 48-78, wherein the menthol comprises 0.2 to 10 % of the composition.

80. The chewing gum according to any of claims 44-75, wherein wherein one or more of flavonoid, xylitol, menthol and metal complexes or metal salts are in the gum phase of the chewing gum.

81. The chewing gum according to any of claims 48-80, wherein wherein wherein one or more of flavonoid, xylitol, menthol and metal complexes or metal salts are in the sorbitol phase of the chewing gum.

82. A method of treatment of a clinical condition relating to common cold or symptoms of a clinical condition relating to common cold in an individual in need thereof, comprising administering to said individual the composition according to any of claims 1 – 43 or the chewing gum according to any of claims 44 to 77.

83. The method according to claim 82, wherein the clinical condition is common cold of the upper and/or lower respiratory tract and/or eyes.

84. The method according to any of claims 82-83, wherein the conditions relating to common cold are viral infections of the upper and/or lower respiratory tract and/or eyes.

85. The method according to any of claims 82-84, wherein the conditions relating to common cold are bacterial infections of the upper and/or lower respiratory tract and/or eyes.

86. The method according to any of claims 82-85, wherein the conditions relating to common cold are allergic conditions of the upper and/or lower respiratory tract and/or eyes.

87. The method according to any of claims 82-86, wherein the conditions relating to common cold are characterized by one or more symptoms of the group comprising coughing, sneezing, muscle pain, sore throat, irritated throat,

hoarseness, headache, malaise, chilliness, fever, nasal discharge, nasal obstruction, pain relating to the sinuses, rhinitis, swelling of mucosal membranes, pharyngitis, asthma, and bronchitis.

88. The method according to any of claims 82-87, wherein the condition relating to common cold is a viral infection caused by or associated with one or more viruses selected from the group consisting of adenoviruses, parvoviruses, picornaviruses, reoviruses, orthomyxoviruses, paramyxoviruses, arenaviruses, caliciviruses, coronaviruses, orthomyxoviruses, rhinovirus, influenza virus, including influenza virus type A and B, echovirus and coxsackie virus.

89. The method according to any of claims 82-88, wherein the condition relating to common cold is a viral infection caused by or associated with one or more viruses selected from the group consisting of coronaviruses and rhinoviruses.

90. The method according to any of claims 82-89, wherein the condition relating to common cold is a bacterial infection caused by or associated with one or more bacteria selected from the group consisting of *Streptococcus pheumoniae,, Streptococcus Haemolyticae, Haemophilus influenxae,* and *Moraxella catarrhalis* or other bacteria present in nasopharynx/oropharynx.

91. The method according to any of claims 82-90, wherein the condition relating to common cold is an allergic condition selected from the group consisting of rhinitis, acute and chronic bronchitis and hay fewer.

92. The method according to any of claims 82-91, wherein the condition related to common cold is an allergic condition characterised by one or more symptoms selected from the group consisting of nasal discharge, nasal congestion, sneezing, cough, swelling of mucosal membranes and rhinitis.

93. The method according to any of claims 82-92, wherein the administration is to the mucosal membrane of the upper and/or lower respiratory tract and/or of the eyes.

94. The method according to any of claims 82-93, wherein the administration is

topical to the mucosal membrane of the oral cavity.

95. A medicament for treating a clinical condition comprising purified flavonoid and purified sugar alcohol or an analogue thereof as active ingredients.

96. The medicament according to claim 95, wherein said sugar alcohol is selected from the group consisting of pentitols and hexitols such as xylitol, mannitol, sorbitol, galacititol (or iditol), dulcitol, ribotol (or adonitol), arabitol (or arabinitol), erythritol, or analogues thereof.

97. The medicament according to any of claims 95-96, wherein the sugar alcohol or an analogue thereof is xylitol or an analogue thereof.

98. The medicament according to any of claims 95–97 further comprising menthol.

99. The medicament according to claim any of claims 95–98 comprising a composition as defined by claims 1 to 47 or a chewing gum as defined by claims 48 to 98.

100. The medicament according to any of claims 95–99, wherein said clinical condition is a condition relating to common cold.

101. The use of one or more purified flavonoids and purified sugar alcohol or analogues thereof for the preparation of a medicament for the treatment of a clinical condition or symptoms of a clinical condition relating to common cold.

Figure 1

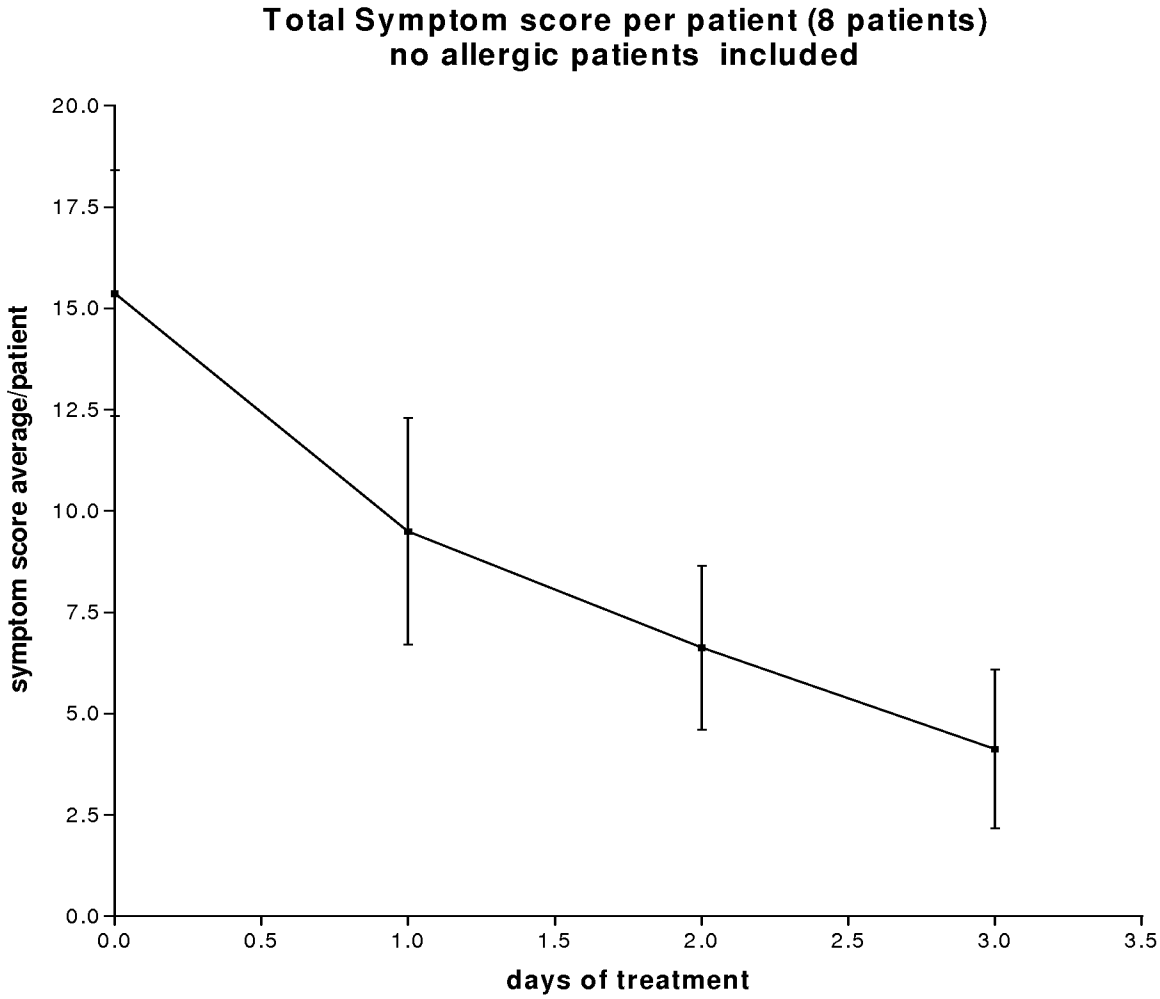
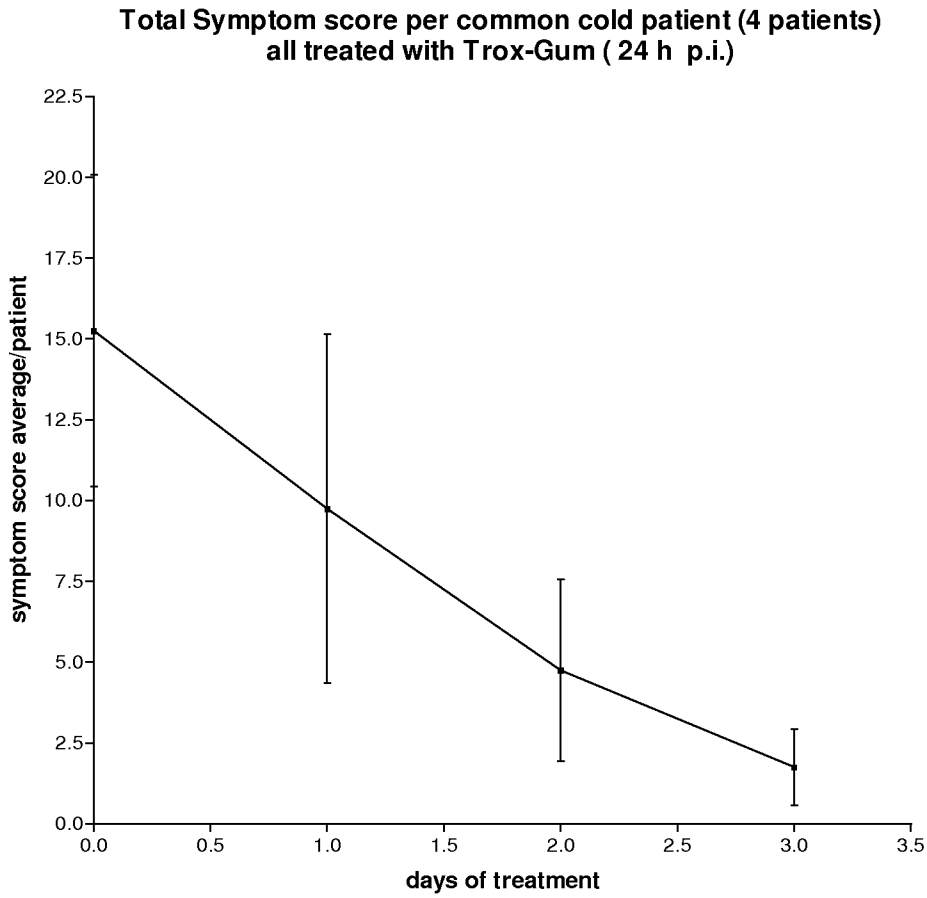
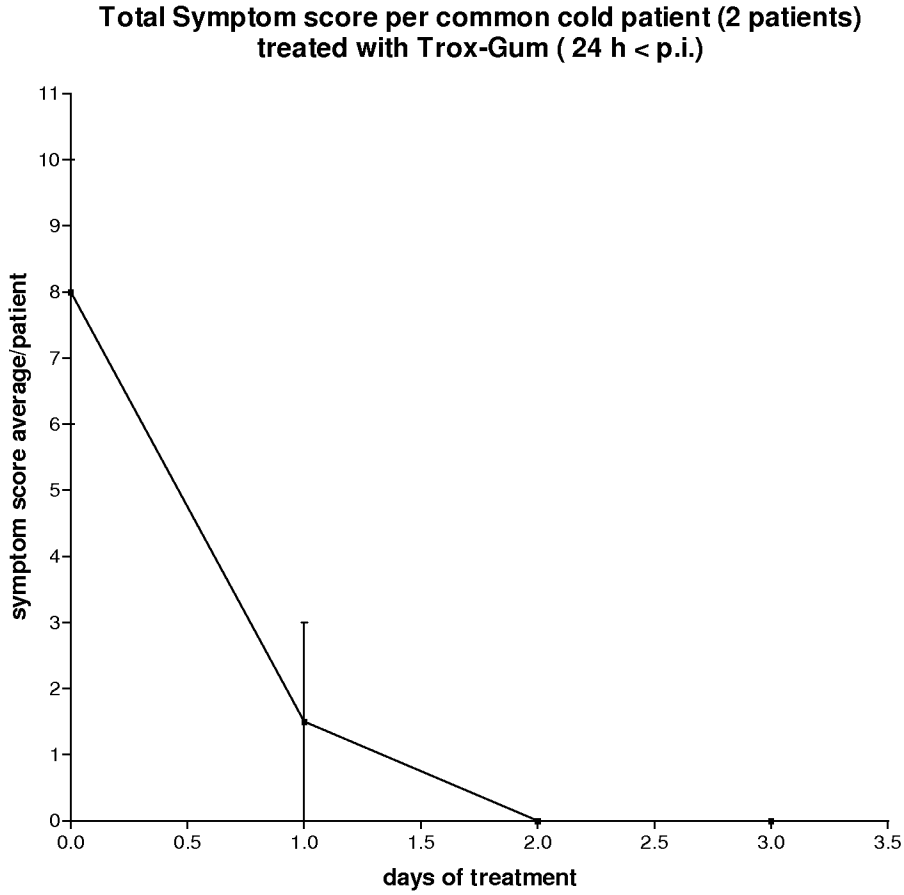

Total Symptom score per patient (8 patients)
no allergic patients included
symptom score average/patient
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
days of treatment

Figure 2



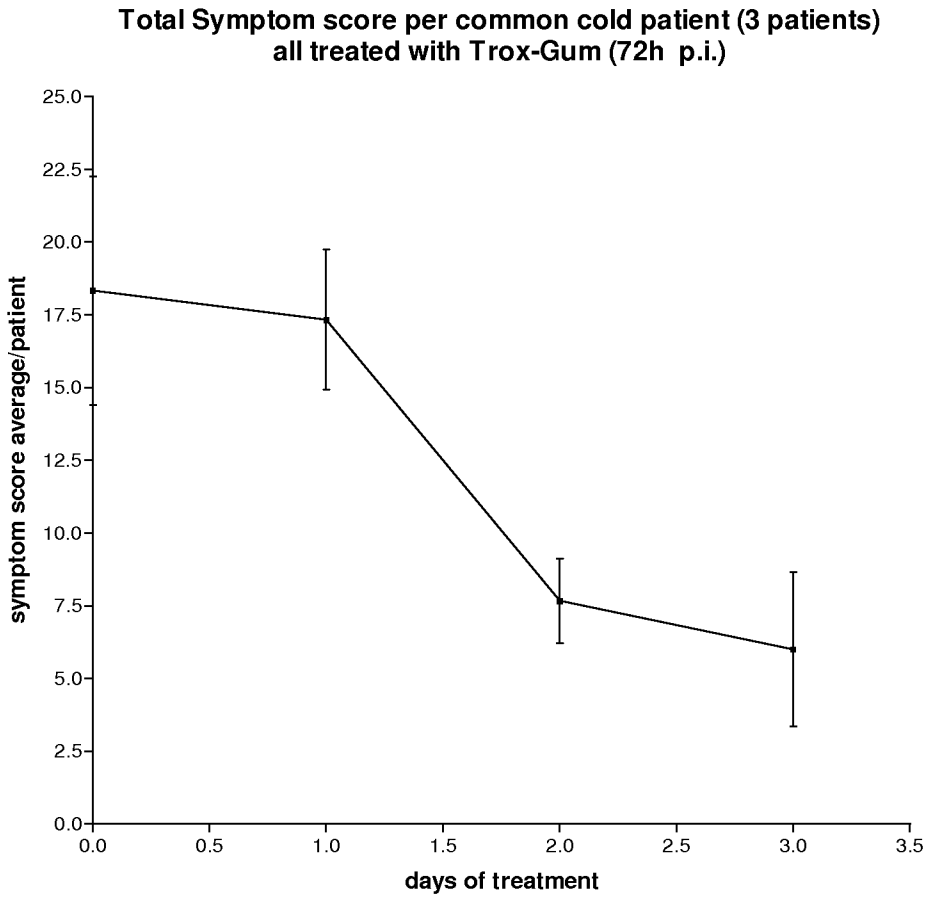
p.i.: common cold patients 24h post infection

Figure 3



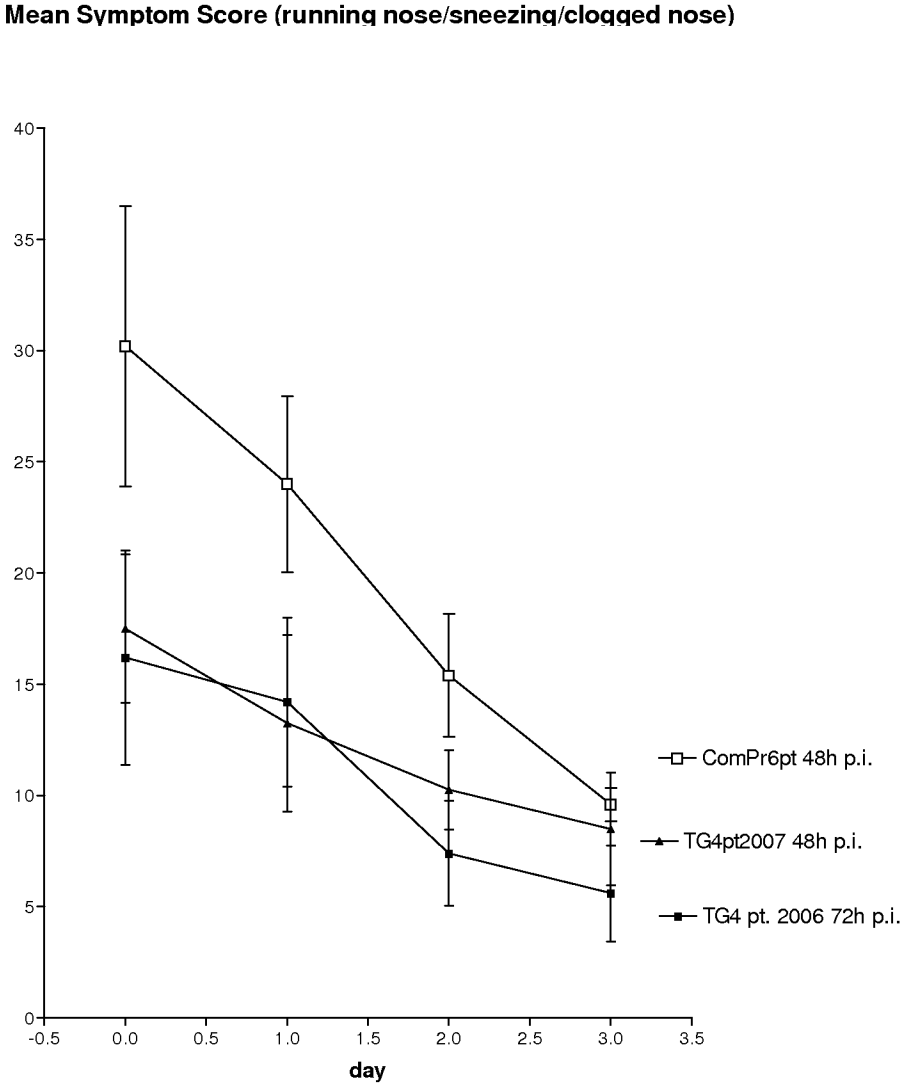
p.i.: common cold patients 24h post infection

Figure 4



p.i.: common cold patients 72h post infection

Figure 5


Mean Symptom Score (running nose/sneezing/clogged nose)
40
35
30
25
20
15
10
5
0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
day
ComPr6pt 48h p.i.
TG4pt2007 48h p.i.
TG4 pt. 2006 72h p.i.