Title: FLAVOURED ORAL DRUG DELIVERY SYSTEM

Abstract: The present invention discloses a flavoured oral drug delivery system susceptible of masking the unpleasant taste of an active substance to be delivered during a delayed, sustained, or immediate release, and a process for the preparation of such a system.
Flavoured oral drug delivery system

Technical Field

The present invention relates to the field of flavoured pharmaceutical compositions. It concerns more particularly a flavoured oral drug delivery system susceptible of masking the unpleasant taste of an active substance to be delivered during a delayed, sustained, or immediate release, and a process for the preparation of such a system.

Background of the Invention

The oral drug delivery products represent an important market of the pharmaceutical industry, as they are the most convenient dosage form to administer, the most cost effective to manufacture, and the most preferred by patients. This oral solid drug dosage form comprises oral controlled (delayed and/or sustained) release products and oral fast dissolving products. Each of these dosage forms provides ease of delivery and is typically cost-effective to manufacture since standard tableting processes and coating technologies are employed. Oral liquid dosage forms such as syrup and dry syrup from solutions, suspensions or emulsions with possible controlled release, are also very popular. They are cheap to manufacture and they are easy to swallow by patients.

The controlled (delayed and/or sustained) release dosage forms are by far the most commonly used for several reasons: they offer once-daily or twice-daily dosing, reduced frequency of side effects, and are cost-effective to manufacture. Delayed release formulations are similar to the sustained release dosage forms in that they "control" the rate and timing of drug release. However, they do not typically provide constant drug delivery for 12 or 24 hours but they delay release of the drug until the dosage form reaches a certain point in the gastrointestinal track. Fast-dissolving solid dosage forms and liquid dosage forms are ideal for patients who are unable to swallow, have difficulties swallowing, or refuse to swallow. Furthermore, in the case of fast-dissolving formulations, patients with busy lifestyles may benefit from these dosage forms, as they do not require water to aid swallowing, nor the use of a dosage device (spoon, syringe). However, for both categories, the active ingredient is in direct contact with the taste buds. Thus, the need for taste-masking is critical.
The problem of masking the unpleasant taste of an active ingredient which is not palatable and which has to be delivered via an oral drug delivery system is always present, whatever the dosage form of the system.

The prior art describes a large number of attempts tending to provide acceptable tasting delivery systems.

More particularly, the problem of providing a palatable form of an oral drug delivery system intended to deliver an unpleasant tasting drug has often been solved by means of a coating for the active ingredient, preventing its early dissolution in the mouth. Materials such as polymers or co-polymers insoluble in water (ethyl cellulose or shellac for instance), or soluble at only certain controlled pH values, are generally used as main constituents of taste-masking coating compositions. The thus obtained coated products may be dosed in varied forms.

For example, JP 200053563 describes bitterness masked microgranules with fast release characteristics. The granules comprise cores containing a pharmacologically active substance with bitter taste; a film coating layer made of water-soluble polymers, and a bitterness masking coating layer containing ethyl cellulose and water-soluble plasticiser. This kind of product is intended to be swallowed and is supposed to mask the bitterness of the active material which will be released once swallowed. This solution to the problem of taste-masking has several drawbacks, notably that it can happen that a part of the active material is released in the mouth before being swallowed, thus creating an unpleasant bitterness in the mouth or a burning sensation in the throat.

Other kinds of dosage forms masking the bitterness of non palatable drugs have been described in the prior art, such as systems in the form of chewable tablets for instance, wherein the unpleasant tasting active substance is again coated so as to be protected, and the dosage form, such as a chewable formulation, is further flavoured. For example, EP 345628 B1 discloses a solid pharmaceutical dosage in a tablet triturate form, which dissolves quickly and masks the taste of the active ingredient. More particularly, the active ingredient is encapsulated in a triglyceride vehicle and the thus obtained particles are uniformly distributed in a porous cementatory network substantially constituted by a carbohydrate. The dosage form includes acceptable excipients, such as flavouring, sweetening and colouring agents. In this disclosure, the dosage form is flavoured in such a way that the chewable tablet tastes pleasant. However, as in the previous case, the active ingredient itself is not flavoured, but is only protected by a coating layer. Consequently, here again, some active ingredient may always be released
in the mouth and thus provoke a bitter taste or burning sensation in the throat. In fact, the film resistance to chewing is low, so that the unpleasant sensations are never fully covered.

Therefore, it appears from the prior art that the problem of taste-masking of active pharmaceutical materials, in any kind of dosage form, has not yet been solved in an efficient way, and that a solution providing an improved system, susceptible of decreasing for instance the typical throat burn of certain bitter active ingredients, is needed.

Description of the Invention

We have now realised an improved taste-masking technology which overcomes the drawbacks existing in the prior art and which provides a solution to the problem of masking unpleasant tasting active materials, in an effective way, suitable for any dosage form of an oral drug delivery system.

One object of the present invention is therefore an oral drug delivery system comprising an unpleasant tasting active substance incorporated in a solid or liquid phase, hereafter referred as the "active phase", characterised in that a neutral flavour is dispersed or solubilized in said phase.

By "neutral flavour", it is understood here an ingredient or a composition susceptible of imparting, modifying or improving the organoleptic properties and/or mouthfeel of a material, without necessarily imparting a specific taste to it. More particularly, the neutral flavour according to the present invention is a flavouring ingredient or a flavouring composition used at a concentration sufficiently low to prevent the perception by the user of any flavour tonality.

The system of the invention is not based on the traditional addition of flavour to a tablet core as disclosed in the prior art, but on the addition of a taste masking flavour, defined as having a neutral taste, directly into the phase comprising the active ingredient, in such a way that the final product, namely solid, soft or liquid particles comprising said active ingredient, also include a taste-masking flavour.

This incorporation presents several advantages. For example, in the case of solid matrix particles, the addition of the neutral flavour advantageously decreases the concentration of the active ingredient at the particle surface as a consequence of a dilution effect. Further, in all the cases where the particles would stay in the mouth or in
the throat, and have time to release some unpleasant tasting active material, concomitant
release of the neutral taste-masking flavour will occur. Thus, a targeted flavour release
system is designed to release the flavour only when and where necessary.

Other advantages of the system of the present invention will appear from the
detailed description and from the accompanying examples.

The delivery system of the invention therefore provides an efficient solution,
applicable to any kind of dosage form and which assures the masking of bitterness or of
any other unpleasant sensation of an active material during its release. Depending on the
dosage form of the final product, the active phase constituted by the active ingredient and
the neutral flavour, in the form of discrete solid, soft or liquid particles, may then be
uniformly dispersed in a support phase which contains excipients required for the release,
preservatives, colouring ingredients of the dosage form, and a second flavour giving the
overall flavour profile to the dosage form.

The oral drug delivery system according to the present invention comprises
an unpleasant tasting active substance incorporated in an active phase, wherein a neutral
flavour is dispersed.

The incorporation in a solid or liquid phase of the active material together
with the neutral flavour may be carried out by way of encapsulation, adsorption, melting
or emulsification. Encapsulation is meant to refer to a variety of conventional techniques
which may be used to provide solid sphere shaped particles, in particular spheroid like,
which uniformly incorporate the active material with the neutral flavour dispersed in a
matrix. Discrete particles are therefore produced by first dispersing or dissolving the
active ingredient and the neutral flavour in a polymeric vehicle (matrix) which
additionally may contain additives to modify the rate and extent of drug release from the
particles. This suspension or solution is then encapsulated. One can cite as non limiting
examples of encapsulation, spray congealing, freeze-drying, spray-coating, wet (e.g.
blender, fluid bed) or dry granulation (for instance compaction), spray-drying and
extrusion, as well as other encapsulation techniques well defined in the art. The active
phase thus obtained, in the form of spheroid particles, provides a uniform distribution of
the active material and of the neutral flavour. Both are retained throughout the matrix in a
homogeneous manner, such that, in case of release, the active material, which texture or
mouthfeel has been modified by the presence of the neutral flavour, is no longer
unpleasant (bitterness, burning sensation) for the patient.
Adsorption is meant to refer to a variety of conventional techniques which may be used to provide stable solid adsorbate complexes which uniformly incorporate the active material with the neutral flavour.

Melting is meant to refer to a variety of conventional techniques which may be used to provide stable solid particles where the active material is finely dispersed or solubilized in a melting carrier. After cooling and milling, uniform calibrated particles incorporating the active material with the neutral flavour are obtained.

The particle size is usually comprised between 10 nm and 2 mm.

The neutral flavour which is incorporated in the active phase, together with the active substance, is capable of improving, modifying or enhancing the organoleptic properties of the latter, while having a tonality which is not readily identifiable. This ingredient is preferably selected from the group consisting of 2-hydroxy-3-methyl-2-cyclopenten-1-one and derivatives, n-octanal, n-decanal, citral, Furaneol® (4-hydroxy-2,5-dimethyl-3(2H)-furanone; origin: Firmenich SA, Geneva, Switzerland), iso-amyl acetate, 2-hydroxy-3-methyl-2-cyclopenten-1-one, vanillin, ethyl-vanillin, acetyl-methylcarbinol, anisic alcohol, methyl furorate, heliotropine, diacetyl, maltol, ethylmaltol, phenylacetic acid and derivatives, animal fat hydrolysate, vegetable oil hydrolysate, anethol, glycyrrhizic acid, lactone derivatives such as delta dodecalactone, delta decalactone, gamma octalactone, gamma decalactone, gamma undecalactone and mixtures thereof. This list is not exhaustive and other ingredients may be used as, or in, the neutral flavouring ingredient according to the invention.

The proportions in which the neutral flavour can be added to the matrix are sufficiently low to prevent the identification of the flavour tonality. The values thus depend on the detection threshold of the flavouring ingredient or composition. As an example, one can cite typical concentrations of the order of 0.1 to 10.0%, possibly more, by weight of compound or composition, relative to the weight of the composition of the phase to which it is added. Lower concentrations than previously mentioned can be used when the compound has a high detection threshold.

Suitable matrix compositions are based on the use of common polymers selected from the group consisting of water insoluble hygroscopic excipients such as micro-crystalline cellulose, powdered cellulose, sodium starch glycolate, cross-linked and non cross-linked polyvinylpyrrolidone, cellulose esters such as cellulose acetate, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose, ethylcellulose, carboxymethyl ethylcellulose, gelatin,
polymethacrylic acid co-polymers such as Eudragit® L30D, Eudragit® NE 30D, Eudragit® RL 30D (origin: Röhm GmbH Degussa-Hüls Gruppe, Kirschenallee, Darmstadt, Germany), comprising or not a plasticizer chosen from the group consisting of glyceryl triacetate, triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, acetyl tributyl citrate, diethyl citrate, dibutyl phthalate, glycerine, triacetin, propylene glycol, polyethylene glycol and mixtures thereof.

Suitable adsorbing agents can be selected from the group consisting of magnesium trisilicate, fumed silica and mixtures thereof.

Suitable carriers for melting can be selected from the group consisting of maltodextrins, saccharose, xylitol, sorbitol, other polyols and mixtures thereof.

Suitable categories of active substances that may be incorporated in the active phase vary widely and generally represent any stable drug composition. Illustrative categories and specific examples include antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlorphenedianol hydrochloride; histamine H1-receptor antagonists, such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate and phenyltoloxamine citrate; histamine H2-receptor antagonists, such as ranitidine, famotidine, cimetidine, nizatidine and roxatidine; decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, hydrochloride ephedrine; various alkaloids, such as codeine phosphate, codeine sulphate and morphine; mineral supplements such as potassium chloride and calcium carbonates, magnesium oxide and other alkali metal and alkaline earth metal salts; laxatives, vitamins; antacids; ion exchange resins such as cholestyramine; anti-cholesterolemic and anti-lipidic agents such as gemfibrozil; antiarrhythmics such as N-acetyl-procainamide; antipyretics such as acetaminophen, aspirin; non steroidal anti inflammatory (NSAI) substances, and more particularly arylcarboxylic derivatives such as ibuprofen, ketoprofen, flurbiprofen, diclofenac, etodolac and naxoprene; NSAI oxamic derivatives such as piroxicam, meloxicam, tenoxicam, NSAI fenamate, indolic, and phenylbutazone derivatives; appetite suppressants such as phenylpropanolamine hydrochloride or caffeine; and expectorants such as guaifenesin. Additional useful active medicaments include coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, gastro-intestinal sedatives and bandages, antidiarrheal and anticonstipate preparations, anti-anginal drugs, vasodilators, anti-hypertensive drugs, vasoconstrictors and migraine treatments, antibiotics, tranquilizers, antiphychotics,
antitumor drugs, anticoagulants, and antithrombotic drugs, hypnotics, sedatives, antiemetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycaemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, antihistaminic or anticholinergic or opiate derivatives (such as codein, dextromethorphan, ethylmorphine, noscapine, pholcodine), cough suppressants, oral mucolytics (such as acetylcisteine, ambroxol, bromhexine, carbocisteine, erdosteine, letosteine), anti-uricemic drugs and the like.

Mixtures of drugs and medicaments may also be used.

According to one embodiment, the active material is constituted by a slightly water soluble bitter active ingredient selected from the group consisting of ibuprofen, ketoprofen, fenoprofen calcium and acetaminophen (origin: Albermarle Corp.). The active phase according to the present invention usually contains from 1 to 90 parts by weight of active substance, preferably from 30 to 90 parts by weight, and from 0.1 to 20 parts by weight of neutral flavour.

Optionally the active phase may also comprise additional ingredients such as sweeteners, colouring agents, anticaking and lubricant agents.

The active phase consisting of particles encapsulating or incorporating the active substance and the neutral flavour is advantageously dispersed in a support phase comprising at least one flavouring ingredient. The latter is intended to give the overall flavour profile to the dosage form. The skilled person in the art is able to choose this flavouring ingredient or composition as a function of the overall taste desired for the dosage form. Non limiting examples of suitable flavours include synthetic flavour oils and/or oils derived from plants, leaves, roots, flowers, fruits, as well as corresponding extracts and combinations thereof. Examples of flavour oils include spearmint oil, peppermint oil, cinnamon oil, or oil of wintergreen. Also useful are artificial natural or synthetic fruit flavours such as citrus oils including lemon, orange, lime, tangerine and grapefruit, and fruit essences including apple, strawberry, cherry, pineapple. Suitable materials can easily be selected by the expert flavorist and can be found in art textbooks such as, for example, Fenarolli's.

The proportions in which the flavouring ingredient is added to the support phase vary in a broad range of values. These values depend on the nature of the support phase and on the organoleptic effect desired, as well as on the nature of the possible co-flavouring ingredients. For instance, concentrations form 0.01 to 10% by weight of the
flavouring compound with respect to the weight of the support phase in which it is incorporated can be used.

In addition to the flavouring ingredient, the support phase may comprise excipients required for the release, the preservation, and/or the colour properties of the dosage form.

Depending on the dosage form of the final product, the support phase may consist of a free flowing or compressed solid, or a liquid.

In another embodiment, the support phase is fast-dissolving in the buccal cavity and is substantially constituted of lactose (Flowlac®; origin: Meggle GmbH, Wasserburg, Germany) and hydrate dextrates.

The system of the invention can be used for example, in the form of a dry or liquid (emulsion or suspension) syrup, a sachet, a chewable, an orodispersible, a dispersible effervescent or a dispersible tablet or a liquid flavour.

In the dosage form, the discrete particles can constitute 0.1 to 70% by weight of the dosage form.

According to one embodiment of the invention, the final product is in the form of a chewable tablet and the support phase is a compressed solid, which may include other adjuvants normally used in the preparation of chewable tablets, including diluants, binders, disintegrants, lubricant, colours and sweeteners.

Another object of the present invention is a process for the preparation of an oral drug delivery system, characterised in that it comprises the step of incorporating an unpleasant tasting active substance in an active solid or liquid phase (referred to as the "active phase"), including a dispersed or solubilized neutral flavour. Preferably, the active substance and the neutral flavour are incorporated in said active phase by way of an encapsulation technique such as those cited above.

In one embodiment of the invention, the active material and the neutral flavour are encapsulated by way of extrusion. The basic process for preparing the solid particles comprises the steps of combining and blending the active substance and the neutral flavour with an extrudable matrix material, an emulsifier and optionally a plasticiser under controlled temperature and stirring conditions useful to produce a uniform melt thereof; extruding the molten mass through a die; chopping and cutting, grinding or pulverising the material obtained as it exits the die or after having cooled the molten mass; and optionally drying. Extrusion processes are described in literature for instance in WO 00/25606, the content of which is hereby included by reference.
According to another embodiment of the invention, the encapsulation of the active material and neutral flavour is effected by wet granulation. More particularly, the process comprises the steps of wet granulating both ingredients with a microcrystalline cellulose composition and then spheronizing the granulation into spheres having a smooth uniform surface, as described in WO 99/17748 hereby included by reference. The discrete particles obtained by encapsulation may then be distributed in a substantially uniform way throughout a support phase, as defined above.

The invention will now be described in greater detail in the following examples, wherein the temperatures are indicated in degrees centigrade and the abbreviations have the usual meaning in the art.

**Embodiments of the Invention**

**Example 1**

Chewable tablets susceptible of delivering ibuprofen

*a) Encapsulation of ibuprofen with a neutral flavour*

A mixture was prepared by admixing ibuprofen (Albemarle Corp.), Avicel® (Sphere Grade, FMC Corporation), and dicalcium phosphate in proportions given in Example 1 of WO 99/17748 here-included by reference. There were added 5% by weight of a neutral vanilla flavour in a spray-dried form, prepared by admixing the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Parts by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanillin</td>
<td>0.8</td>
</tr>
<tr>
<td>Ethylvanillin</td>
<td>2.5</td>
</tr>
<tr>
<td>Heliotropine</td>
<td>0.3</td>
</tr>
<tr>
<td>Triacetin</td>
<td>13.1</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>83.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
To this dry mixture, there were added 30% of water for granulation. The thus obtained blend was extruded and further spheronized according to usual techniques as described for instance in WO 99/17748.

5 b) *Preparation of a chewable tablet*

The chewable tablet was prepared as described in Example 2 of WO 99/17748, using the solid spheres prepared according to a).

10 Example 2

Comparative example on orodispersible tablets susceptible of delivering quinine

a) *Preparation of the unpleasant tasting active substance, namely quinine coated sugar spheres*

A mixture was prepared by admixing 25 g of quinine hydrochloride (origin: Chemische Fabrik Schweizerh, Basel, Switzerland) in a 250 ml aqueous solution of starch at 1.8% w/w. The solution had a total load of quinine hydrochloride of 10.80%. This solution was then sprayed on sugar spheres (suglets; origin: NP Pharm SA, Bazainville, France) in a Strea 1 Niro aeromatic spray dryer (origin: Aeromatic Fielder AG, Switzerland).

b) *Preparation of the active phase comprising flavoured taste-masked (FTM) quinine sugar spheres*

A spraying solution comprising the neutral flavour was prepared as follows: 200 ml of water were placed in a beaker, to which 3.08 g of sodium lauryl sulfate (origin: Henkel KGaA, Düsseldorf, Germany) and 6.60 g of dibutyl sebacate (origin: Fluka) were further added. The mixture was then slowly stirred in 44 g of Eudragit® EPO (origin: Röhm GmbH Degussa-Hüls Gruppe, Kirschenalle, Darmstadt, Germany) with a propeller stirrer to avoid lump formation. After 2 hours of continued stirring to ensure total solubilisation of the polymer, 1.17 g of a spray-dried caramel neutral flavour were added to the solution. Said flavour comprised the following ingredients:
Ingredients & Parts by weight

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Parts by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetymethylcarbinol</td>
<td>5.3</td>
</tr>
<tr>
<td>Vanillin</td>
<td>5.3</td>
</tr>
<tr>
<td>Maltol</td>
<td>1.5</td>
</tr>
<tr>
<td>Heliotropine</td>
<td>1.2</td>
</tr>
<tr>
<td>Anisic alcohol</td>
<td>0.9</td>
</tr>
<tr>
<td>Methyl furoate</td>
<td>0.7</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>1.8</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>83.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

The active particles prepared under a) were partly (55 g) placed in a pan coating and blend with 125 g of uncoated sugar spheres.

The spraying solution comprising the neutral flavour was sprayed on separate blends of sugar spheres thus forming a flavoured taste-masked active ingredient.

c) *Preparation of unflavoured taste-masked quinine sugar spheres (blank)*

The same procedure described under b) was used but no flavour was added to the spraying solution.

d) *Preparation of an orodispersible tablet*

Orodispersible tablets were prepared from respectively, 48 mg of non taste-masked (NTM) quinine sugar spheres a), 64 mg of flavoured taste-masked (FTM) quinine sugar spheres b), and 52 mg of unflavoured taste-masked (UTM) quinine sugar spheres c), using the following base per tablet:

Ingredients & Mg per tablet

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mg per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flowlac® 1)</td>
<td>830.0</td>
</tr>
<tr>
<td>Hydrate dextrate</td>
<td>500.0</td>
</tr>
<tr>
<td>Aspartam®</td>
<td>10.7</td>
</tr>
<tr>
<td>Acesulfam® K</td>
<td>5.3</td>
</tr>
<tr>
<td>Flavour fruit of forest 2)</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1348.0</strong></td>
</tr>
</tbody>
</table>
1) origin: Meggle GmbH, Wasserburg, Germany
2) 501161 AP 0551; origin: Firmenich SA, Geneva, Switzerland

The quantities of NTM, FTM and UTM were chosen in order to ensure that the tablets a), b), and c), contained similar quinine load.

The orodispersible tablets a), b) and c) were evaluated on a blind test by a panel of 6 people. The 6 persons established that the taste-masking was clearly improved from NTM to FTM products.

Example 3

Comparative example on orodispersible tablets susceptible of delivering quinine

Example 2 was repeated, flavouring the taste-masked quinine spheres of step b) with 1.40 g of a liquid flavour comprising the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Parts by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>64.2</td>
</tr>
<tr>
<td>Anethol</td>
<td>7.5</td>
</tr>
<tr>
<td>Vanillin</td>
<td>4.0</td>
</tr>
<tr>
<td>Delta decalactone</td>
<td>3.0</td>
</tr>
<tr>
<td>Ethylvanillin</td>
<td>3.0</td>
</tr>
<tr>
<td>Furaneol® 1)</td>
<td>3.0</td>
</tr>
<tr>
<td>Isoamyl acetate</td>
<td>2.0</td>
</tr>
<tr>
<td>Delta dodecalactone</td>
<td>2.0</td>
</tr>
<tr>
<td>Glycyrrhizic acid</td>
<td>2.0</td>
</tr>
<tr>
<td>Heliotropine</td>
<td>2.0</td>
</tr>
<tr>
<td>Acetyl methylcarbinol</td>
<td>1.5</td>
</tr>
<tr>
<td>Maltol</td>
<td>1.5</td>
</tr>
<tr>
<td>Methylcyclopentenolone 2)</td>
<td>1.5</td>
</tr>
<tr>
<td>Gamma decalactone</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Gamma octalactone 1.0
Phenylacetic acid 0.3
Total 100.0

5 1) 4-hydroxy-2,5-dimethyl-3(2H)-furanone; origin: Firmenich SA, Geneva, Switzerland
2) 2-hydroxy-3-methyl-2-cyclopenten-1-one

On a blind test, among the 6 people forming the evaluation panel, all of them found that the FTM product was more pleasant and did not exhibit any bitterness by comparison with the NTM product.

Example 4

Comparative example on solid dosage forms of quinine

a) Adsorption of quinine hydrochloride and neutral flavour on a solid phase

A solution was prepared by admixing 37 g of quinine hydrochloride (origin: Chemische Fabrik Schweizerh, Basel, Switzerland) with 100 g of propylene glycol and 175 ml of water, 1.90 g of a neutral flavour were added to this solution. Said flavour comprised the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Parts by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl acetate</td>
<td>2.0</td>
</tr>
<tr>
<td>Acetilmethyl-carbinol</td>
<td>1.5</td>
</tr>
<tr>
<td>Phenylacetic acid</td>
<td>0.3</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>42.0</td>
</tr>
<tr>
<td>Anethol</td>
<td>7.5</td>
</tr>
<tr>
<td>Delta decalactone</td>
<td>3.0</td>
</tr>
<tr>
<td>Maltol</td>
<td>1.5</td>
</tr>
<tr>
<td>Delta dodecalactone</td>
<td>2.0</td>
</tr>
<tr>
<td>Gamma decalactone</td>
<td>1.0</td>
</tr>
<tr>
<td>Diacetyl</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Propylene glycol 24.2
Ethyl vanillin 3.0
Furaneol\(^{1)}\) 3.0
Heliotropine 2.0
5 2-Hydroxy-3-methyl-2-cyclopenten-1-one 1.5
Gamma octalactone 0.5
Vanillin 4.0
Total 100.0

10 1) 4-hydroxy-2,5-dimethyl-3(2H)-furanone ; origin: Firmenich SA, Geneva, Switzerland

On the other hand, a mixture of 100 g of Cab-o-Sil EH5 (Sigma-Aldrich) and 100 g of magnesium trisilicate adsorbate (Fluka), was charged on a high shear mixer, to which the initial solution was added slowly. Adsorbate granules were then prepared, following the procedure described in Example 1 of WO 95/03785, the contents of which is hereby included by reference.

b) Adsorption of quinine hydrochloride on a solid phase

The same procedure as that described under a) was followed to prepare adsorbate granules without any neutral flavour in the initial solution.

c) Preparation of solid dosage forms of quinine

The respective "active phases" constituted by the granules prepared under a) and b) were independently incorporated in a support phase of the following composition:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Mg per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruv(^{\circledast})</td>
<td>14</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>7</td>
</tr>
<tr>
<td>Aspartam(^{\circledast})</td>
<td>84</td>
</tr>
<tr>
<td>Acesulfam(^{\circledast}) K</td>
<td>42</td>
</tr>
<tr>
<td>Flowlac(^{\circledast}) 1)</td>
<td>746</td>
</tr>
<tr>
<td>Hydrate dextrate</td>
<td>448</td>
</tr>
<tr>
<td>Flavour</td>
<td>Quantity</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Strawberry flavour</td>
<td>8</td>
</tr>
<tr>
<td>Adsorbed quinine with/without neutral flavour</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>1364</td>
</tr>
</tbody>
</table>

5 1) see Example 2
2) 501098 AP 0551; origin: Firmenich SA, Geneva, Switzerland

Two kinds of delivery systems were thus obtained, namely the first one containing a neutral flavour incorporated in its active phase (hereafter referred as sample a)) and the other one, having an active phase free of neutral flavour (hereafter referred as sample b)).

d) Comparative samples

For the purposes of the comparison, further to a) and b), two other delivery systems, c), and d) were prepared (using the same ingredients and same proportions for the support phase):

c) wherein the active phase comprised the hydrochloride quinine as such (i.e. not adsorbed on a carrier), and the support phase was flavoured with a mixture of strawberry flavour and neutral flavour.

d) wherein the active phase comprised the hydrochloride quinine as such (i.e. not adsorbed on a carrier), and the support phase was flavoured with strawberry flavour.

The four delivery systems there-prepared, a), b), c), and d) were evaluated on a blind test by a panel of 15 people who were asked to evaluate on the one hand, the bitterness of the samples and on the other, the flavour intensity of the samples, on a scale ranging from 1 (lowest bitterness/flavour intensity) to 10 (highest bitterness/flavour intensity).
The bar diagrams reported on page 1/1 (Fig. 1 and Fig. 2) give the results of these evaluations.

The diagram reporting the flavour intensity (Fig. 2) shows that the neutral flavour does not significantly influence the flavour intensity, whatever the phase where it is incorporated, which confirms its "neutral" nature, i.e. the fact that it cannot be perceived as such in the final product.

On the other hand, the diagram reporting the bitterness evaluation (Fig. 1) clearly demonstrates the bitterness masking effect of the neutral flavour present in the active phase. More particularly, it can be stated firstly that the bitterness is perceived almost equally intensively when there is no neutral flavour (d)) or when the neutral flavour is in the support phase (c)). In other words, the neutral flavour has no effect on bitterness evaluation when added to the support phase. Furthermore, the bitterness, which is already perceived less intensively when the active phase is constituted by quinine adsorbed on the carrier (b)), is perceived even weaker to the panellists when the active phase comprises the neutral flavour adsorbed with quinine on the porous carrier (a)). The positive effect of the neutral flavour incorporated directly in the active phase is thus demonstrated.
Claims

1. Oral drug delivery system comprising an unpleasant tasting active substance incorporated in an active solid or liquid phase, characterised in that a neutral flavour is dispersed or solubilized in said phase.

2. Oral drug delivery system according to claim 1, characterised in that the active substance is encapsulated, adsorbed or dispersed in the active phase.

3. Oral drug delivery system according to claim 2, characterised in that the active substance is encapsulated by a process of extrusion, spray drying, or wet or dry granulation, spray congealing, freeze drying, fluidized bed granulation, agglomeration or spray-coating.

4. Oral drug delivery system according to claim 2, characterised in that the active substance is adsorbed on a carrier.

5. Oral drug delivery system according to claim 2, characterised in that the active substance is dispersed on a carrier by a process of melting or emulsification.

6. Oral drug delivery system according to claim 1, characterised in that the active phase is dispersed throughout a support phase comprising at least one flavouring ingredient.

7. Oral drug delivery system according to claim 6, characterised in that the support phase is a free flowing solid or a compressed solid or a liquid.

8. Oral drug delivery system according to claim 6, characterised in that the support phase is constituted of lactose and hydrate dextrates.

9. Oral drug delivery system according to any one of claims 1 to 8, characterised in that the neutral flavour is selected from the group consisting of 2-hydroxy-3-methyl-2-cyclopenten-1-one and derivatives, n-octanal, n-decanal, citral, Furaneol® (4-hydroxy-2,5-dimethyl-3(2H)-furanone), isoamyl acetate, vanillin, ethylvanillin, acetylmethylcarbinol, anisic alcohol, methyl furate, heliotropine, diacetyl, maltol, ethylmaltol, phenylacetic acid and derivatives, animal fat hydrolysate, vegetable oil hydrolysate, anethol, glycerrhizic acid, lactone derivatives such as delta dodecalactone, delta decalactone, gamma octalactone, gamma decalactone, gamma undecalactone.

10. Oral drug delivery system according to any one of claims 1 to 9, characterised in that the amount of neutral flavour in the active phase is comprised between 0.1 and 10 parts by weight, with respect to the total composition of the active phase.
11. Oral drug delivery system according to any one of claims 1 to 10, in the form of a dry or liquid syrup, a sachet, a chewable, an orodispersible, a dispersible effervescent or a dispersible tablet.

12. Process for the preparation of an oral drug delivery system, characterised in that it comprises the step of incorporating an unpleasant tasting active substance in a phase including a dispersed or solubilised neutral flavour.

13. Process according to claim 12, characterised in that the incorporation of the active substance consists in a process selected from the group consisting of extrusion, wet or dry granulation, spray drying, spray congealing, freeze drying, fluidised bed granulation, agglomeration, spray coating, melting or emulsification.

14. Process according to claim 13, characterised in that it comprises the step of dispersing the active phase in a flavoured support phase.

15. Process according to any one of claims 12 to 14, characterised in that the unpleasant tasting active substance is incorporated in a matrix comprising the neutral flavour and in that said matrix is extruded.