Title: TASTE MASKED PHARMACEUTICAL COMPOSITIONS

Abstract: This invention comprises an unpleasant-taste-masked pharmaceutical composition for oral consumption comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s, at least one sweetener and optionally one or more of diluents/bulking agents, excipients/adjuvants and flavors. In one embodiment of the unpleasant-taste-masked pharmaceutical composition, the sweetener in the agglomerate comprises at least a high intensity sweetener; or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener. An embodiment of the unpleasant-taste-masked pharmaceutical composition may further comprise a coating of a water insoluble material on the agglomerate wherein the thickness of the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type II apparatus. The unpleasant-taste-masked pharmaceutical composition of this invention may further comprise at least one thickener in the agglomerate. The unpleasant-taste-masked pharmaceutical composition of this invention may also comprise at least one binding agent in the agglomerate or/and may also comprise effervescence generating means. In the context of this invention, unpleasant taste comprises bitter taste and any other taste that is repulsive for oral consumption. The pharmaceutical composition of this invention may be an orodispersible or water dispersible composition. The invention also comprises methods of making the compositions of this invention.
TITLE
TASTE MASKED PHARMACEUTICAL COMPOSITIONS.

TECHNICAL FIELD
The present invention describes composition and preparation techniques for quick dissolving taste masked granules for pharmaceutical active. The invention pertains to orodispersible granules and tablets, effervescent granules and tablets, water dispersible granules and tablets and chewable tablets. The invention also pertains to taste masking of bitter/unpleasant-tasting drugs including Acetaminophen and Phenylephrine hydrochloride, and a method of making taste masked granules of pharmaceutical actives and dosage forms.

BACKGROUND OF THE INVENTION
For many years, oral route has been the most acceptable route of drug administration. This is due to many advantages of this route such as convenience of administration, non-invasive nature and ability to accommodate numerous drugs. The compressed tablet is most widely used and prescribed for oral administration. However, it has several disadvantages. For example, it is estimated that 50% of the population have problems swallowing tablets; it is hard for aged persons to swallow tablets or to medicate children who are unable or unwilling to swallow tablets. This leads to poor, even non-compliance with the treatment and thus has a negative impact on the efficacy of the treatment. The conventional tablet dosage form is also inconvenient for the 'people on the move' who often do not have access to drinking water or fluids.
To overcome these limitations, in last decade solid dosage forms such as chewable tablets; orodispersible powders and tablets; and effervescent powders and tablets; and dispersible powders and tablets have been developed and commercialized. Among them, orodispersible powders and tablets have been drawing attention in recent years from the view point of its user-friendliness, because it can be taken easily even by a patient who has a difficulty in swallowing, and also without water. However, being a dosage form which is immediately disintegrated or dispersible in the oral cavity, the attempts to conceal/mask the unpleasant taste had always remained an unsolved problem for a very long time. The most obvious approach of simple addition of sweeteners to the mix of solid dosage formulation has never given a completely successful result. Further attempts have been done by coating the drug substance have been unsuccessful for a number of reasons. First, the coating themselves often contain defects that result in the leaking or transfer of taste of the unpleasant tasting active ingredients to the person taking the drug. Second, this method may also alter the release profile or bioavailability of the drug substance. Thus, it would be desirable to provide compositions and methods for bitterness masking or unpleasant-taste masking technique for the quickly dispersible dosage forms in the oral cavity which is considered to be effective for a drug having an unpleasant taste, particularly a strong bitterness.

US 4,800,087 discloses microcapsule based controlled release taste-masked pharmaceutical formulation

US 4,865,851 discloses A composition comprising cefuroxime axetil in particulate form, the particles being provided with integral coatings of a lipid or a mixture of lipids which are insoluble in water and which serve to mask the bitter taste of
cefuroximeaxetil upon oral administration but which disperse or dissolve on contact with gastro-intestinal fluid.

US 4,916,161 discloses a process for preparing tablets containing a foul tasting pharmaceutical agent in which the bad taste of the agent is effectively masked comprising the steps of: (a) wet-granulating a dry particulate pre-granulation blend comprising the agent and hydroxypropyl methylcellulose phthalate with an aqueous granulating composition in which said hydroxypropyl methylcellulose phthalate is at least partially soluble to form: a granulation containing the agent; (b) grinding and drying the product of Step (a); (c) blending the product of step (b) with tablet adjuvants; and (d) compressing the product of step (c) to produce tablets.

US 4,940,588 and US 4,952,402 disclose taste masked powders, but they relate to controlled release powders and do not teach anything on how to get taste masked powders that are not controlled release.

US 5,013,716 discloses an unpleasant taste masking composition which comprises a medicament drug having a bitter taste or unpleasant off-note and a chlorodeoxysugar derivative selected from the group consisting of chlorodeoxysucrose derivatives and chlorodeoxygalactosucrose derivatives and mixtures thereof in an amount from about 0.001% to about 5.0%, by weight to nullify the taste or unpleasant off-note of the medicament drug. The patent, however, illustrates a chewing gum composition only and does not provide any teaching on how to make orally consumable pharmaceutical compositions that are not chewing gums.

US 5,057,319 discloses a pharmaceutical granule composition of Cimetidine wherein an ester of a polyhydroxy compound said polyhydroxy compound being a non-
polymeric, non-aromatic hydrocarbon or carbohydrate having at least 2 hydroxyl groups per molecule is used as a taste masking agent.

US 5,084,278 discloses a microcapsule based chewable pharmaceutical taste masked composition, however, the same is a controlled release composition.

US 5,407,921 has disclosed a method for suppressing a bitter taste of a material to be placed in the mouth or in contact with the mouth, which comprises adding a bitter taste suppressing effective amount of a composition selected from the group consisting of acidic phospholipids or acidic lysophospholipids to the material, wherein the neutral lipid content of the composition is not more than 30 wt. % and the neutral phospholipid content of the composition is not more than 50 wt. %

US 5,552,152 has disclosed microcapsule based chewable taste masked tablet, however, the same is a controlled release dosage form.

Thus, there was a need of making a composition of pharmaceutical powder composition for oral consumption comprising at least one pharmaceutical active compound of unpleasant taste wherein unpleasant taste masking is achieved wherein the composition releases more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus.

SUMMARY OF INVENTION

This invention comprises an unpleasant-taste-masked pharmaceutical composition for oral consumption comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s, at least one sweetener and optionally one or
more of diluents /bulking agents, excipients/adjuvents and flavors. In one
embodiment of this invention, the sweetener in the agglomerate comprises at least a
high intensity sweetener; or a mixture of one or more of low intensity sweetener and
at least one high intensity sweetener. The Pharmaceutical composition of this
invention may further comprise a coating of a water insoluble material on the
agglomerate wherein the thickness of the coating is strong enough to prevent release
of unpleasant taste on tongue when orally administered but release more than 80% of
the pharmaceutically active unpleasant tasting compound in 15 minutes when
subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2
apparatus. The unpleasant-taste-masked pharmaceutical composition of this
invention may further comprise at least one thickener in the agglomerate. The
unpleasant-taste-masked pharmaceutical composition of this invention comprising an
agglomerate of the pharmaceutically active compound/s, at least one sweetener and
optionally one or more of diluents /bulking agents, excipients/adjuvents and flavors
may also comprise at least one binding agent in the agglomerate. The unpleasant-
taste-masked pharmaceutical composition of this invention comprising an
agglomerate of the pharmaceutically active compound/s, at least one sweetener and
optionally one or more of diluents /bulking agents may also comprise effervescence
generating means.

In the context of this invention, unpleasant taste comprises bitter taste and any other
taste that is repulsive for oral consumption. The pharmaceutical composition of this
invention may be an orodispersible or water dispersible composition.
In one embodiment of this invention, the unpleasant-taste-masked pharmaceutical composition of this invention may comprise, as percentage of the composition, Phenylephrine hydrochloride 0.5% to 50%, Mannitol 5% to 90%, Sucralose 0.1% to 5%, xylitol 5% to 60%, Mannitol 5% to 90%, microcrystalline cellulose 1% to 70%.

In another embodiment, this invention comprises a method of preparing an unpleasant-taste-masked pharmaceutical composition comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener; wherein: (a) the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener; (b) the method comprising steps of: (i) dissolving one or more low intensity sweetener, the pharmaceutically active compound and the high intensity sweetener in water, (ii) preparing a powder composition of one or more low intensity sweeteners and a pharmaceutically acceptable diluent/bulking agent, (iii) granulating composition of step ii, with composition of step i in a granulator to get an agglomerate, drying the agglomerate in a drier, (iv) unloading the dried agglomerate, milling and sifting to get uniformly sized taste masked granules of the agglomerate composition, and (v) optionally filling the agglomerate composition in sachets. In this method, low intensity sweetener may be dissolved in water by warming, the unpleasant tasting pharmaceutically active compound and the high intensity sweetener may be dissolved under stirring, the granulated composition may be dried in a drier till the stage when loss on drying (LOD) is less than 4%, and sifting may be done through a #40 sieve.
In yet another embodiment of this invention comprises an unpleasant-taste-masked pharmaceutical composition comprising, as percentage of the composition, Acetaminophen 10% to 90%, Mannitol 5% to 90%, Sucralose 0.1% to 5%, a plasticized 25% w/w aqueous dispersion containing ethyl cellulose, ammonium hydroxide, medium chain triglycerides & Oleic acid with a pH of about 9.5-11.5, Citric acid 0.3%, Sorbitol (powder) 5% to 70%, Maltodextrin 1% to 50%, Sodium Bicarbonate 0.25-% to 10%, licorice extract as ammonia salt of Glycyrrhizic Acid 0.1% to 10%, and pharmaceutically permissible flavors 0.25% to 5%.

An additional embodiment of this invention comprises a method of preparing an unpleasant-taste-masked pharmaceutical composition comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener; wherein: (a) the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener, (b) the agglomerate comprises a coating of a water insoluble material on the same wherein the thickness of the coating is strong enough to prevent immediate release of unpleasant taste on tongue when orally administered but releases more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus, (c) the method comprising steps of: (i) dissolving the pharmaceutically active compound in a volatile organic solvent, (ii) dissolving a low intensity sweetener and a high intensity sweetener in water, (iii) transferring composition of Step i. and ii. into a vacuum
dryer and to get dry agglomerate, (iv) milling and sifting the dry agglomerate, (v) coating the agglomerate with a water insoluble material to get taste masked agglomerate granules, (vi) mixing the agglomerate granules of step v. with excipients or/and adjuvents, and (vii) optionally filling in sachets.

In a further embodiment, this invention comprises an unpleasant-taste-masked pharmaceutical composition comprising, as percentage of the composition, Acetaminophen 10 to 90 %, Sodium carboxymethylcellulose 5 to 50%, Sucralose 0.1 to 5 %, Cellulose acetate 0.5 to 10 %, sodium chloride 0.1 to 2.0 %, Mannitol 5 to 90 %, Xylitol 5 to 60%, Sorbitol 5 to 70%, Magnesium Stearate 0.5 to 5.0%, pharmacetically permissible flavors 0.1 to 5% Licorice extract as ammonia salt of Glycyrrhizic Acid 0.1 to 10 %.

In a further embodiment, this invention comprises a method of making unpleasant-taste-masked pharmaceutical composition comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener; wherein: (a) the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener, (b) the agglomerate further comprising a hydrophilic thickener incorporated in the agglomerate, (c) the agglomerate is coated with a water insoluble material on the agglomerate wherein the thickness of the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus, (d) the method comprising steps of: (i)
making gel mass of a thickener in water, (ii) adding the pharmaceutically active compound to the gel mass, (iii) adding high intensity sweetener to the gel mass of the thickener, (iv) drying the gel mass to get dry agglomerate, (v) milling and sifting the agglomerate through sieve, (vi) dissolving water insoluble material in one or a mixture of volatile organic solvent/s and coating the dried agglomerate with a coat of a water insoluble material such that the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus, (vii) optionally adding excipients, and (viii) optionally filling the powder in sachets.

In yet another embodiment, this invention comprises an unpleasant-taste-masked pharmaceutical composition of claim 5 comprising, as percentage of the composition, Acetaminophen 10 to 90%, Mannitol 5 to 90%, sucralose 0.1 to 5%, Polyvinylpyrrolidone (PVP K 30) 0.25 to 5%, Titanium dioxide 0.25 to 5%, pharmaceutically permissible color 0.01 to 2%, Maltodextrin 5 to 50%, sodium benzoate 0.1 to 2% and pharmaceutically permissible flavor 0.1 to 5%.

In another embodiment this invention comprises a method of making an unpleasant-taste-masked pharmaceutical composition of claim 5 comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener, wherein: (a) the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener, (b) further comprising at least
one binding polymer in the agglomerate; (c) the method comprising following steps of: (i) dissolving the pharmaceutically active compound in a volatile organic solvent, (ii) dissolving a low intensity sweetener and high intensity sweetener in water, (iii) transferring composition of step i. and step ii. into a vacuum dryer and drying into an agglomerate having moisture content less than 2%, (iv) after drying, milling and sifting the agglomerate and mixing with colorants, (v) granulating the above dried agglomerate with binding solution prepared with a water insoluble binding agent, (vi) blending the dried agglomerate granules with fillers and excipients, (vii) optionally filling the blend in sachets.

One more embodiment of this invention comprises an unpleasant-taste-masked pharmaceutical composition of claim 6 comprising, as percentage of the composition: acetaminophen 10 to 90%, Mannitol 5 to 90%, Sucralose 0.1 to 5%, Citric acid 0.25 to 10%, Sodium bicarbonate 1 to 30%, Sorbitol powder 5 to 70%, Maltodextrin 5 to 50%, Licorice extract as ammonia salt of Glycyrrhizic Acid 0.1 to 10% and Pharmaceutically permissible flavor 0.1 to 5%.

Yet one more embodiment of this invention comprises a method of making an unpleasant-taste-masked pharmaceutical composition comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener, further comprising effervescence generating means; the method comprising steps of: (a) dissolving the pharmaceutically active compound in a volatile organic solvent and transferring into a vacuum dryer, (b) adding and dissolving a food acid and an alkali capable of producing effervescence when contacted with water, (c) dissolving a high intensity sweetener and a low intensity
sweetener into the above organic solvent containing the ingredients added above and
drying the whole composition in the vacuum dryer to get an agglomerate, (d) sifting
the dried agglomerate through a mesh, (e) adding fillers and excipients to the
agglomerate, mixing well, (f) optionally filling the above blended powder into
sachets.

DETAILS OF INVENTION

For the purpose of this specification, "Agglomerate" is defined as "a mass or
collection of things" that are in particulate form, the components of which are so
intimately associated with each other that in a process of oral consumption of a
pharmaceutical composition that is in the form of an orodispersible or water
dispersible powder or tablet, the aggregates forming a component of such a
pharmaceutical form disperse from a tablet or a powder composition in oral cavity or
in water as intact particles, do not release taste of the unpleasantly tasting component
immediately and the components of the aggregate separate from each other enough
to release unpleasant taste only when they reach stomach."

For the purpose of this specification, taste masking comprises absence of release of
an unfavorable taste from and orally administered composition of solid powder or a
tablet that is orodispersible or water dispersible, remains in the buckle cavity for a
period of time ordinarily required for oral administration of orodissolvable powders
or orodissolvable tablets for holding in the mouth before following action of
swallowing it. The target is to make sure that the unpleasant taste or flavor is not
released until the composition is on the tongue, however, after its swallowing the
drug is released within such a time in the stomach that its release profile is not
modified in a significant way when compared to release profile of the same drug when orally administered as such. It is considered that this requirement is satisfied if in a dissolution test 80% or more drug is released from a composition in 15 minutes in USP Type 2 apparatus.

Thus, the pharmaceutical compositions of this invention have either significantly reduced unpleasant taste or show a total masking of unpleasant taste.

One embodiment of taste masked pharmaceutical composition of the present invention comprises a dried mixture/agglomerate of a drug substance, thickening agent and a sweetener; the said dried mixture/agglomerate is coated with a water insoluble material. One embodiment of method of preparation of this composition comprises steps of heating purified water, preferably to 60°C, adding a thickener to the hot water with stirring, continuing stirring till a gel mass is formed, adding a drug substance slowly into the above said gel mass under stirring and adding a high intensity sweetener and mixing for sufficient time to get translucent gel mass, drying the gel mass, preferably until the Loss on Drying (LOD) is less than 4 %, milling the dried material, sizing, coating the sized composition with a solution of cellulose acetate in one or more of volatile solvent/s, drying and sizing, blending with powders of sized excipients and filling in sachets. In one illustrative embodiment, the drug is Acetaminophen, known widely by name "Paracetamol", thickener is Sodium carboxymethylcellulose (Sodium CMC), the high intensity sweetener includes sucralose, drying includes drying under reduced pressure, sizing includes passing through a # 40 mesh, the water insoluble material used in coating solution includes cellulose acetate, solvent/s used to dissolve water insoluble material includes Isopropyl alcohol and Dichloromethane and excipients include Sodium Chloride,
Mannitol, Xylitol, Sorbitol, Magnasweet (MM135), Magnesium stearate, Powdarome Lemon premium Flavour and Blackcurrant Flavour (20.4561.IP PHA).

This embodiment of the taste masked drug composition and method of making the same has been illustrated in a non-limiting Example 1 disclosed below.

Another embodiment of the present invention provides for a taste masked pharmaceutical composition comprises a mixture or agglomerate of drug substance and one or more sweeteners; the said mixture/agglomerate being coated with a water insoluble film forming material. In one embodiment of method of preparing this composition comprises steps of dissolving separately the drug substance and one or more sweeteners in a suitable solvent, drying to provide an agglomerate, coating the agglomerate with a water insoluble film forming material. In one embodiment, the water insoluble material may be an aqueous dispersion of ethyl cellulose. Surelease® E-7-19040 Clear is one such formulation commercially available which is based on aqueous dispersion of Ethyl cellulose that has been used in illustrations in this specification. After coating, the material was sifted through 40 mesh to get uniformly sized taste masked granules. This embodiment of the product and method of making the same is illustrated by Example 2 below.

A further embodiment of this invention comprises a sized composition of solid agglomerated particles with Loss on drying (LOD) of less than 2% comprising a drug that is desired to be taste masked, one or more of sweetener/s and one or more of suitable diluents/bulking agents. Preferably sizing is done through 40 mesh. An embodiment of a method of preparation of this composition comprises steps of preparing an aqueous solution from the drug desired to be taste masked (Preferably Phenylephrine hydrochloride in non-limiting example 3), mixing with a mixture of
one or more of sweeteners and further with one or more diluents/bulking agents result into wet agglomerate. The high intensity sweetener includes sucralose, the low intensity sweetener having low glycemic index may be a polyol, including, without limitation, Mannitol. And an adsorbent not limiting to Microcrystalline cellulose.

The wet agglomerate is dried till LOD is less than 2% and sized. Preferably sizing is done through 40 mesh. This embodiment of the composition and method of its making is illustrated by a non-limiting Example 3 disclosed below. The composition of this embodiment may be mixed with excipients /adjuvents and flavors.

The excipients /adjuvents and flavors include, without limitation, Sodium Chloride, Mannitol, Xylitol, Sorbitol, Citric acid, Magnasweet (MM 135), Magnesium stearate, Powdarome Lemon Premium, Blackcurrant Flavour (20.4561.1P PHA) and the like. The resulting composition may be filled in sachets.

Another embodiment of the present invention comprises of agglomerate of a drug substance that needs to be taste masked, one or more of sweeteners, a low intensity sweetener having low glycemic index, effervescence generating means, flavors and pharmaceutically permitted excipients. The low intensity sweetener having low glycemic index may be a polyol, including, without limitation, Mannitol. The effervescence generating means may be a mixture of Citric acid and Sodium bicarbonate, the composition may be filled into a sachet. One embodiment of a method of preparation of this composition comprises steps of dissolving the drug substance intended to be taste masked in a low boiling volatile organic solvent, adding effervescence generating means, high intensity sweetener and a low intensity sweetener having low glycemic index to provide a sweetening bulk without adding significant calories, removing the solvent by evaporation and drying to the LOD less than 2% and sized.
than 2%, sizing the material by passing through a 40 mesh and adding excipients. The embodiment of this composition and method of producing the same has been illustrated in Example 5, wherein the drug is Acetaminophen, the solvent is ethanol, evaporation is preferably done in a Rotocone Vacuum Dryer, effervescence generating means is a mixture of citric acid and sodium bicarbonate, high intensity sweetener of choice is preferably sucralose and polyol of choice is Mannitol, sizing is done by passing through # 40 mesh, excipients added comprise Maltodextrin, Sorbitol powder, Magnasweet (MM 135), and Strawberry Flavour, all sifted through # 40 mesh, blended for 15 minutes and filled into sachets. This embodiment of the composition of taste masked drug and method of its preparation is illustrated by Example 5 below.

In a yet another embodiment of the present invention comprises dried mixture or agglomerate of drug substance and one or more of sweeteners and the said mixture/agglomerate being granulated with a binding solution and colorants. One embodiment of a method of preparation of this composition comprises steps of dissolving the drug needed to be taste masked in a volatile solvent, dissolving low calorie low intensity sweetener and a high intensity sweetener in water, mixing the two solutions and drying them by evaporation till the LOD is less than 2%, milling and sizing by passing through a sieve, granulating the dry sized composition and an optional colorant with a binding solution containing a polymer, drying, sizing by passing through a sieve and blending with excipients. Without limitation, the volatile solvent may include isopropanol, low calorie low intensity sweetener may include mannitol, high intensity sweetener may include sucralose, polymer used in binding solution may be Povidone K-30® (Polyvinylpyrrolidone with K value 30)
including a commercially available compositions of soluble Polyvinylpyrrolidones under Trade-names Plasdone® K-29/32, Kollidon® 30.

Colorant may be Titanium Dioxide and Sunset yellow FCF, sizing includes sifting through # 40 mesh and excipients include Maltodextrin, Sodium Benzoate and Orange juice flavor. The blend may be filled in sachets. The embodiment of this composition and method of its preparation is illustrated by non-limiting Example 6 disclosed below.

In an embodiment of the taste masked pharmaceutical composition of this invention, the thickening agent selected comprises water soluble polymers, hydrocolloids and gums including, without limitation, one or more of Hydroxypropylmethyl cellulose, Hydroxypropyl cellulose, Hydroxypropylethyl cellulose, Sodium carboxymethylcellulose, Xanthan gum, Acacia, Guar gum, Sodium Alginate, Alginic acid and Tragacanth etc.

In one embodiment, the composition of this invention comprises, without limitation, could be one or more of sweeteners, including but not limited to, Sucrose, Mannitol, Dextrose, Fructose, Sucralose, Monoammonium Glycerohizinate and Aspartame.

In addition to film forming water insoluble material illustrated in the examples given below, any pharmaceutically acceptable alternative water insoluble material or waxy material may be used comprising, without limitation, one or more of Cellulose Acetate, ethylcellulose, co-polymers of acrylic and methacrylic acid esters, cellulose acetate butyrate, cellulose acetate triacetate, Glycerol dibehenate, Polyethylene glycols, Glycerol dipalmitostearate, Propylene glycol monocaprylate, Glycerol behenate and mixtures thereof. Commercially available water insoluble materials
include for example, Ethocel® available from Dow Chemical Corp., aqueous polymeric dispersions such as Aquacoat® (about 30% w/w aqueous dispersion containing ethyl cellulose, Sodium lauryl sulfate, cetyl alcohol and hydrogen peroxide with a pH of about 4.0-7.0) available from FMC BioPolymer, 1735 Market street, Philadelphia, PA 19103, USA., and Surelease® E-7-19040 Clear (a plasticized 25% w/w aqueous dispersion containing ethyl cellulose, ammonium hydroxide, medium chain triglycerides & Oleic acid with a pH of about 9.5-11.5) available from Colorcon; Polyvinyl acetate, cellulose acetate butyrate, and copolymers of polymethacrylic acid available from Rohm Pharma GmbH under the trade name Eudragit® (e.g., Eudragit L30D55®, Eudragit L100-55®, Eudragit RS 30D®, Eudragit RL 30D® and Eudragit EPO®).

The coating of the drug mixture or agglomerate may be done by granulation in Planetary mixer or in Rapid mixer granulator, followed by drying in a Fluid bed dryer or Tray dryer; or by spray techniques in a Fluidized bed processor. The granules or coated granules of the present invention may be mixed with one or more sweeteners, flavors and other suitable excipients to make orodispersible granules or tablets, effervescent granules or tablets, water dispersible granules or tablets, and chewable tablets.

A taste masked pharmaceutical composition of this invention may also be prepared in the form of a film that is capable of disintegrating in a buccal cavity. The film formers that could be used for making such a film comprise, without limitation, one or more of, a Cellulose Acetate, Ethylcellulose, Polyvinyl alcohol, Hydroxypropylmethyl cellulose, hydroxypropyl cellulose, gelatin and the like.
In one embodiment, the binding agent in the formulation of this invention may be
selected, one or more, from the group comprising Polyvinylpyrrolidone, Starch, Hydroxypropyl cellulose, gelatin and the like.

The compositions of this invention comprises a coating that are applied such that they do not significantly alter the release of the drug substance or its bioavailability when compared to the uncoated drug product as illustrated in a dissolution test, which showed release of more than 80% of Acetaminophen in 15 minutes.

The composition of this invention may have only one drug or may be a combi-preparation containing more than one drug that are permitted as combi-preparation and all or only some of them requiring taste masking. A combi-preparation has been illustrated in Example 4.

The examples given below are only illustrative of working of this invention and do not limit in any way the scope of this invention. All variations and equivalents obvious to a person skilled in the art are included within the scope of this invention.

Although the examples given are for Acetaminophen and Phenylephrine hydrochloride which are bitter/unpleasant, the invention applies to all unpleasant tasting pharmaceutical actives, whether bitter/unpleasant or otherwise including, without limitations, Aspirin, ibuprofen, dexibuprofen lysinate, naproxen, ketoprofen, lactam, quinolone, macrolide and salts thereof, loperamide, famotidine, ranitidine, cimetidine and salts thereof, ibersartan, captopril, lisinopril and salts thereof, nefzodone, Ondansetron HCl, Theophylline, Benzethonium chloride, Caffeine, Pheylpropanolamine, cephalexin, Midazolam, Clindamycin, Omeprazole, Dexamethasone, Phenobarbital, Dicloxacillin, Prednisolone, Furosemide,

The high intensity sweetener used in this invention may comprise, without limitation, Sucralose, Aspartame, Acesulfame potassium, Cyclamate, Glycyrrhizin, Neotame Neohesperidin Dihydrochalcone (NHDC), Alitame, Saccharin, Stevia (Stevioside and Rebaudioside A), Thaumatin and mixtures thereof.

The low intensity sweetener may comprise, without limitation, Glucose, Lactose, Fructose, Sucrose, Mannose, Mannitol, Sorbitol, Xylitol, Erythritol, Inositol, Isomalt, Maltitol, Tagatose and mixtures thereof.

The thickener may comprise, without limitations, Gum Acacia, Agar, Alginic acid, Carrageenan, Gelatin, Gaur gum, Dextrin, Sodium carboxymethyl cellulose, Sodium Alginate, Arabinan, Fructan, Fuctan, Galactan, Galacturan, Glucan, Mannan, Xylan, Levan, Fucoidan, Carrageenan, Galactocarolose, Pectin, Amylose, Pullulan, Glycogen, Amylopectin, Dextran, Dextrin, Pustulan, Chitin, Xanthan gum, Guar gum, Gum tragacanth and mixtures thereof.
The bulking agents may comprise Starch, Lactose, Powdered Cellulose, Sucrose, Microcrystalline Cellulose, Mannitol, Calcium Phosphate, Sorbitol, maltodextrin and mixtures thereof.

The effervescence generating means may comprise, without limitations, citric acid or tartaric acid with sodium bicarbonate or calcium carbonate and mixtures thereof.

The binding agent may comprise Sucrose, Liquid glucose, Gum Acacia Gum Tragacanth, Gelatin, Starch Paste, Pregelatinized Starch, Alginic Acid, Cellulose, Methyl Cellulose, Ethyl Cellulose, HydroxyPropyl Methyl Cellulose (HPMC), HydroxyPropyl Cellulose, Sodium CarboxyMethylCellulose, Polyvinyl Pyrrolidone (PVP), Polyethylene Glycol (PEG), Polyvinyl Alcohols, Polymethacrylates and mixtures thereof.

Throughout this specification, "High Intensity Sweetener" pertains to sweeteners that for same weight by weight basis, are 10 times or more sweeter than sucrose [10 time or more of sucrose equivalent sweetness (SES)]; and "Low Intensity Sweetener" pertains to sweeteners that for same weight by weight basis, less than 10 times sweetness of sucrose [less than 10 time sucrose equivalent sweetness (SES)].

**EXAMPLE 1**

A DRIED MIXTURE/AGGLOMERATE OF A DRUG SUBSTANCE, THICKENING AGENT AND A SWEETENER; THE SAID DRIED MIXTURE/AGGLOMERATE COATED WITH A WATER INSOLUBLE MATERIAL:

*Acetaminophen orodispersible powder*

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>MATERIAL NAME</th>
<th>QUANTITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetaminophen</td>
<td>25.000</td>
</tr>
</tbody>
</table>
A flavor further containing arabic Gum E414, Maltodextrin, Propylene glycol E 1520 (8% max) Available from KERRY INGREDIENTS AND FLAVOURS ITALIA SPA Via Capitani di Mozzo 12/16 1-24030 Mozzo (BG) - Italy:

http://www.kerry.com/

Licorice extract, a sweetener available from MAFCO WORLDWIDE CORPORATION THIRD STREET & JEFFERSON AVENUE 300 JEFFERSON STREET CAMDEN, NEW JERSEY USA 08104

http://www.mandfworldwide.com/Subsidiaries/mafco_worldwide_co rp.htm

Procedure:

1. Purified water was heated to about 60°C and Sodium carboxymethylcellulose (Sodium CMC) was added to it under stirring. Stirring was continued till it forms a gel mass.
2. Acetaminophen was added slowly to the above under stirring.

3. Sucralose was dissolved in water and added to the above under stirring. The above gel mass was unloaded and dried in a vacuum drier till the Loss on drying (LOD) is less than 4% to get an agglomerate.

4. The dried agglomerate was sifted through 40 mesh.

5. Coating solution was prepared by dissolving Cellulose acetate in Isopropyl alcohol and Dichloromethane.

6. The dried and sifted material of step no. 5 was coated with coating solution of step no. 6. Isopropyl alcohol and Dichloromethane were allowed to evaporate and the coated material was sifted through #40 mesh.

7. Excipients like Sodium Chloride, Mannitol, Xylitol, Sorbitol, Magnasweet (MM135), Magnesium stearate, Powdarome Lemon Premium, and Blackcurrant Flavour (20.456 LIP PHA) were sifted through 40 mesh and blended along with the above granules in a blender.

8. The granules were filled in sachets.

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.

EXAMPLE 2

A MIXTURE OR AGGLOMERATE OF DRUG SUBSTANCE AND ONE OR MORE SWEETENERS; THE SAID MIXTURE/AGGLOMERATE BEING COATED WITH A WATER INSOLUBLE FILM FORMING MATERIAL:
Acetaminophen orodispersible powder

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>MATERIAL NAME</th>
<th>QUANTITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetaminophen</td>
<td>25.00</td>
</tr>
<tr>
<td>2</td>
<td>Isopropyl alcohol</td>
<td>QS</td>
</tr>
<tr>
<td>3</td>
<td>Mannitol</td>
<td>50.00</td>
</tr>
<tr>
<td>4</td>
<td>Sucralose</td>
<td>1.000</td>
</tr>
<tr>
<td>5</td>
<td>Purified water</td>
<td>QS</td>
</tr>
<tr>
<td>6</td>
<td>Surelease E-7-19040 Clear§</td>
<td>3.808</td>
</tr>
<tr>
<td>7</td>
<td>Citric acid</td>
<td>0.300</td>
</tr>
<tr>
<td>8</td>
<td>Sorbitol (powder)</td>
<td>12.642</td>
</tr>
<tr>
<td>9</td>
<td>Maltodextrin</td>
<td>5.000</td>
</tr>
<tr>
<td>10</td>
<td>Sodium bicarbonate</td>
<td>0.500</td>
</tr>
<tr>
<td>11</td>
<td>Magnasweet (MM135) (ammonia salt of Glycyrrhizic Acid)§§</td>
<td>0.250</td>
</tr>
<tr>
<td>12</td>
<td>Orange juice flavor Permaseal (PHS 133147)§§§</td>
<td>1.000</td>
</tr>
<tr>
<td>13</td>
<td>Powdarome Lemon Premium §§§§</td>
<td>0.500</td>
</tr>
</tbody>
</table>

§ a plasticized 25% w/w aqueous dispersion containing ethyl cellulose, ammonium hydroxide, medium chain triglycerides & Oleic acid with a pH of about 9.5-1 1.5

§§ Licorice extract, a sweetener available from MAFCO WORLDWIDE CORPORATION THIRD STREET & JEFFERSON AVENUE 300 JEFFERSON STREET CAMDEN, NEW JERSEY USA 08104

http://www.mandfworldwide.com/Subsidiaries/mafco_worldwide_corp.htm

§§§ A pale yellow to yellow, fruity, sweet, citrus Juicy fine powder. Available from Givaudan Singapore Pte Ltd 1 Woodlands Ave 8, Singapore 738972, Singapore.
http://www.givaudan.com/Singapore.qm @givaudan.com

§§§§ An off white to pale yellow colored powder of Natural flavoring substance. Available from Firmenich Aromatics (India) Pvt. Ltd. Unit-II Survey 57/3, (6, 8 & 9) Daman Bhenlore Rd, Village Dunetha, Daman 396210, UT, India.
http://www.firmenich.com/

Procedure:

1. Acetaminophen was dissolved in Isopropyl alcohol.

2. Mannitol and Sucralose were dissolved in Purified water.

3. Step 1 and 2 were transferred into Rotacone Vacuum Dryer and dried till the LOD is less than 2% to get an agglomerate.
4. After drying, the agglomerate was unloaded, milled and sifted through # 40 mesh.

5. The # 40 mesh particles of step no. 4 were coated with Surelease® E-7-19040 Clear (a platform of complete, aqueous coating system utilizing ethylcellulose as the polymer and the dried coated agglomerate was sifted through 40 mesh to get uniformly sized taste masked granules. Excipient/adjuvants, including but not limited to Xylitol, Citric acid, Sorbitol powder, Sucralose, Magnasweet, Sodium bicarbonate, Magnesium Stearate and Orange juice flavor Permaseal (PHS 133147). The materials were sifted through 40 mesh and blended along with taste masked granules in a blender, and

6. filled in to sachets.

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.

EXAMPLE 3

A SIZED COMPOSITION OF SOLID AGGLOMERATED PARTICLES WITH LOSS ON DRYING (LOD) OF LESS THAN 2% COMPRISING A DRUG THAT IS DESIRED TO BE TASTE MASKED, ONE OR MORE OF SWEETENER/S AND ONE OR MORE OF SUITABLE DILUENTS/BULKING AGENTS:
Taste masked granules of Phenylephrine Hydrochloride

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>MATERIAL NAME</th>
<th>QUANTITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenylephrine Hydrochloride</td>
<td>2.905</td>
</tr>
<tr>
<td>2</td>
<td>Mannitol</td>
<td>14.286</td>
</tr>
<tr>
<td>3</td>
<td>Sucralose</td>
<td>0.810</td>
</tr>
<tr>
<td>4</td>
<td>Purified water</td>
<td>Qs</td>
</tr>
<tr>
<td>5</td>
<td>Xylitol</td>
<td>27.714</td>
</tr>
<tr>
<td>6</td>
<td>Mannitol</td>
<td>16.667</td>
</tr>
<tr>
<td>7</td>
<td>Microcrystalline Cellulose</td>
<td>37.619</td>
</tr>
</tbody>
</table>

Procedure:

1. Mannitol was dissolved in warm water (approx. 50°C) and Phenylephrine Hydrochloride and Sucralose were added to dissolve in it under stirring.

2. Xylitol, Mannitol and Microcrystalline cellulose were sifted through 40 mesh.

3. Composition of step 2 was agglomerated by granulation with composition of step 1 in a granulator and dried in a drier till the loss on drying (LOD) is less than 2% to get an agglomerate.

4. After drying, the agglomerate was unloaded, milled and sifted through 40 mesh to get uniformly sized taste masked granules

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.
EXAMPLE 4

Acetaminophen and Phenylephrine Hydrochloride orodispersible powder

The taste masked granules of Phenylephrine Hydrochloride (example 3) were mixed with Taste masked granules of Acetaminophen (example 2) and filled into sachets.

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.

EXAMPLE 5

Agglomerate of a drug substance that needs to be taste masked, one or more of sweeteners, a low intensity sweetener having low glycemic index, effervescence generating means, flavors and pharmaceutically permitted excipients:

Acetaminophen orodispersible powder

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>MATERIAL NAME</th>
<th>QUANTITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetaminophen</td>
<td>25.000</td>
</tr>
<tr>
<td>2</td>
<td>Mannitol</td>
<td>45.000</td>
</tr>
<tr>
<td>3</td>
<td>Sucralose</td>
<td>0.750</td>
</tr>
<tr>
<td>4</td>
<td>Ethanol</td>
<td>QS</td>
</tr>
<tr>
<td>5</td>
<td>Citric acid</td>
<td>3.250</td>
</tr>
<tr>
<td>6</td>
<td>Sodium Bicarbonate</td>
<td>10.950</td>
</tr>
<tr>
<td>7</td>
<td>Sorbitol powder</td>
<td>8.000</td>
</tr>
<tr>
<td>8</td>
<td>Maltodextrin</td>
<td>6.250</td>
</tr>
<tr>
<td>9</td>
<td>Magnasweet (MM135)§</td>
<td>0.300</td>
</tr>
<tr>
<td>10</td>
<td>Strawberry Cream Flavor Permaseal (11407--31)$§§</td>
<td>0.500</td>
</tr>
</tbody>
</table>
Licorice extract, a sweetener available from MAFCO WORLDWIDE CORPORATION THIRD STREET & JEFFERSON AVENUE 300 JEFFERSON STREET CAMDEN, NEW JERSEY USA 08104
http://www.mandfworldwide.com/Subsidiaries/ afco_worldwide_corp.htm

§§ Off white to pale yellow coloured powder available from Givaudan Singapore Pte Ltd 1 Woodlands Ave 8, Singapore 738972, Singapore. http://www.givaudan.com/ Singapore.qm @givaudan.com

1. Acetaminophen was dissolved in Ethanol and transferred into Rotocone Vacuum dryer (RCVD).
2. Citric acid was added to the above and stirred to get clear solution.
3. Sodium bicarbonate was added to it and mixed for 15-20 minutes.
4. Sucralose and Mannitol were transferred into the above Rotacone Vacuum Dryer and dried till the loss on drying (LOD) is less than 2% to get an agglomerate.
5. The dried agglomerate was sifted through #40 mesh.
6. Maltodextrin, Sorbitol powder, Magna sweet (MM 135), and Strawberry flavour were sifted through #40 mesh.
7. The materials of step 5 and 6 were loaded into blender and mixed for 15 minutes
8. The above blended powder was filled into sachets.

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.
EXAMPLE 6

DRIED MIXTURE OR AGGLOMERATE OF DRUG SUBSTANCE, ONE OR MORE OF SWEETENERS AND ONE OR MORE COLURANTS, AND THE SAID MIXTURE/AGGLOMERATE BEING GRANULATED WITH A BINDING AGENT

Preparation of Acetaminophen dispersible powder

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>MATERIAL NAME</th>
<th>QUANTITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetaminophen</td>
<td>25.000</td>
</tr>
<tr>
<td>2</td>
<td>Isopropyl alcohol</td>
<td>QS</td>
</tr>
<tr>
<td>3</td>
<td>Mannitol</td>
<td>50.000</td>
</tr>
<tr>
<td>4</td>
<td>Sucralose</td>
<td>1.000</td>
</tr>
<tr>
<td>5</td>
<td>Purified water</td>
<td>QS</td>
</tr>
<tr>
<td>6</td>
<td>Povidone (K 30)§</td>
<td>0.250</td>
</tr>
<tr>
<td>7</td>
<td>Titanium dioxide</td>
<td>1.000</td>
</tr>
<tr>
<td>8</td>
<td>Sunset yellow FCF</td>
<td>0.150</td>
</tr>
<tr>
<td>9</td>
<td>Purified water</td>
<td>QS</td>
</tr>
<tr>
<td>10</td>
<td>Maltodextrin</td>
<td>20.850</td>
</tr>
<tr>
<td>11</td>
<td>Sodium Benzoate</td>
<td>0.250</td>
</tr>
<tr>
<td>12</td>
<td>Orange juice flavor Permaseal (PHS 133147)§§</td>
<td>1.50</td>
</tr>
</tbody>
</table>

§ Polyvinylpyrrolidone with K value 30

A pale yellow to yellow, fruity, sweet, citrus Juicy fine powder. Available from Givaudan Singapore Pte Ltd 1 Woodlands Ave 8, Singapore 738972, Singapore.

http://www.givaudan.com/Singapore.qm @givaudan.com

1. Acetaminophen was dissolved in Isopropyl alcohol.
2. Mannitol and Sucralose were dissolved in Purified water.
3. Step 1 and 2 were transferred into Rotacone Vacuum Dryer and dried till the Loss on drying (LOD) is less than 2% to get an agglomerate.
4. After drying, the agglomerate was milled and sifted through # 40 mesh and was mixed with # 100 mesh passed titanium dioxide and sunset yellow FCF.
5. The above mixture was granulated with binding solution (prepared with a binding agent Povidone K-30® purified water) in a granulator and dried in a drier to produce agglomerate granules containing the binding agent.

6. The dried agglomerate granules were sifted through # 40 mesh and loaded into a blender.

7. Maltodextrin, Sodium Benzoate and Orange juice flavor Permaseal (PHS 133147) were sifted through # 40 mesh and loaded into the same above blender and mixed for 15 minutes.

8. The blend was filled in Sachets.

Mixture of above ingredients done without agglomeration tasted bitter/unpleasant whereas bitter/unpleasant taste was masked in the agglomerated granules as made above.

**Example 7: Dissolution Test**

Dissolution test was performed on examples 1, 2, 3, 4, 5, and 6 in USP Type 2 apparatus at 50 RPM in Phosphate Buffer pH 5.8 and it was found that a substantial amount (more than 80%) of drug was released in 15 minutes from all the formulations.
CLAIMS

1. An unpleasant-taste-masked pharmaceutical composition for oral consumption comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s, at least one sweetener and optionally one or more of diluents /bulking agents, excipients/adjuvents and flavors.

2. The pharmaceutical composition of claim 1 wherein the sweetener in the agglomerate comprises at least a high intensity sweetener; or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener.

3. The Pharmaceutical composition of claim 2 further comprising a coating of a water insoluble material on the agglomerate wherein the thickness of the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus.

4. The Pharmaceutical composition of claim 3 further comprising at least one thickener in the agglomerate.

5. The pharmaceutical composition of claim 1 further comprising at least one binding agent in the agglomerate.

6. The pharmaceutical composition of claim 1 further comprising effervescence generating means.

7. The pharmaceutical composition of any one of above claims 1, or 2 or 3 or 4 or 5 or 6, wherein:
a. unpleasant taste comprises bitter taste and any other taste that is repulsive for oral consumption,

b. the pharmaceutical composition is an orodispensible or water dispersible composition,

c. the pharmaceutically active compound of unpleasant taste comprises Acetaminophen, Phenylephrine hydrochloride, Aspirin, Ibuprofen, dexibuprofen lysinate, naproxen, ketoprofen, lactam, quinolone, macrolide and salts thereof, loperamide, famotidine, ranitidine, cimetidine and salts thereof, ibersartan, captopril, lisinopril and salts thereof, nefzodone, Ondansetron Hcl, Theophylline, Benzethonium chloride, Caffeine, Pheylpropanolamine, cephalexin, Midazolam, Clindamycin, Omeprazole, Dexamethasone, Phenobarbital, Dicloxacillin Prednisolone, Furosemide, Prednisone, Iron Sulfate Metronidazole, Metoclopramide HCl, Ofloxacin, Norfloxacin, Fluonazole, Azithromycin, Clarithromycin, Roxithromycin, Tramadol, Folic Acid, Anticholesterolomic saponins, Levofoxacin, Ciprofloxacin, Sildenafil citrate, Dextromethorphan hydrobromide, Ampicillin trihydrate, Nizatidine, Roxithromycin, Clarithromycin, Chloroquine diphosphate, Metronidazole, Dextromethorphan Hydrobromide, buspirone and salts thereof, chlorpheniramine, astemizole, pseudoephedrine, antivirals, anticancer, antiplatelet, vitamins, minerals, psyllium and mixtures thereof,
d. the excipients/adjuvants comprise one or more selected from the group Xylitol, Citric acid, Sorbitol powder, Sucralose, Magnasweet, Sodium bicarbonate, Magnesium Stearate,
e. the high intensity sweetener comprises one or more of sucralose, Aspartame, Acesulfame potassium, Cyclamate, Glycyrrhizin, Neotame, Neohesperidin Dihydrochalcone (NHDC), Alitame, Saccharin, Stevia (Stevioside and Rebaudioside A), Thaumatin and mixtures thereof,
f. the low intensity sweetener comprises one or more of Glucose, Lactose, Fructose, Sucrose, Mannose, Mannitol, Sorbitol, Xylitol, Erythritol, Inositol, Isomalt, Maltitol, Tagatose,
g. the water insoluble material comprises one or more of water insoluble polymers or waxy materials further comprising ethyl cellulose, co-polymers of acrylic and methacrylic acid esters, cellulose acetate, cellulose acetate butyrate, cellulose acetate triacetate, Glycerol dibehenate, Polyethylene glycols, Glycerol dipalmitostearate, Propylene glycol monocaprylate, Glycerol behenate and mixtures thereof,
h. the thickener comprises water soluble polymers, hydrocolloids and gums, which may be one or more selected from the group hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, Acacia, Agar, Alginic acid, Carrageenan, Gelatin, Gaur gum, Dextrin, Sodium carboxymethyl cellulose, Sodium alginate, arabinan, fructan, fuctan, galactan,
galacturan, glucan, mannan, xylan, levan, fucoidan, carrageenan, galactocarolose, pectin, amylose, pullulan, glycogen, amylpectin, dextran, dextrin, pustulan, chitin, xanthan gum, and tragacanth and mixtures thereof,

i. the diluent/bulking agent comprises Starch, Lactose, Powdered Cellulose, Sucrose, Microcrystalline Cellulose, Mannitol, Calcium Phosphate, Sorbitol, maltodextrin and mixtures thereof,

j. effervescence generating means comprises citric acid or tartaric acid with sodium bicarbonate or calcium carbonate and mixtures thereof,

k. the binding agent comprises Sucrose, Liquid glucose, Gum Acacia Gum Tragacanth, Gelatin, Starch Paste, Pregelatinized Starch, Alginic Acid, Cellulose, Methyl Cellulose, Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose, Sodium Carboxy Methyl Cellulose, Polyvinyl Pyrrolidone (PVP), Polyethylene Glycol (PEG), Polyvinyl Alcohols, Polymethacrylates, and mixtures thereof.

8. The unpleasant-taste-masked pharmaceutical composition of claim 2 comprising, as percentage of the composition, Phenylephrine hydrochloride 0.5% to 50%, Mannitol 5% to 90%, Sucralose 0.1% to 5%, xylitol 5% to 60%, Mannitol 5% to 90%, microcrystalline cellulose 1% to 70%.

9. A method of preparing an unpleasant-taste-masked pharmaceutical composition comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical
composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener; wherein:

(a) the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener;

(b) the method comprising steps of:

i. dissolving one or more low intensity sweetener, the pharmaceutically active compound and the high intensity sweetener in water,

ii. preparing a powder composition of one or more low intensity sweeteners and a pharmaceutically acceptable diluent/bulking agent,

iii. granulating composition of step ii, with composition of step i in a granulator to get an agglomerate, drying the agglomerate in a drier,

iv. unloading the dried agglomerate, milling and sifting to get uniformly sized taste masked granules of the agglomerate composition,

v. optionally filling the agglomerate composition in sachets.

10. The method of preparing a pharmaceutical composition of claim 9 wherein:

a. water is warmed for dissolution of Mannitol as low intensity sweetener, Phenylephrine Hydrochloride as unpleasant tasting pharmaceutically active compound, Sucralose as high intensity sweetener and dissolution is done under stirring,
b. the composition of step b. of claim 9 comprises Xylitol, Mannitol and the pharmaceutically acceptable filler comprises Microcrystalline cellulose,

c. the granulated composition of step c. of claim 9 is dried in a drier till the stage when loss on drying (LOD) is less than 2%,

d. sifting is done through a #40 sieve.

11. The unpleasant-taste-masked pharmaceutical composition of claim 3 comprising, as percentage of the composition, Acetaminophen 10% to 90%, Mannitol 5% to 90%, Sucralose 0.1% to 5%, a plasticized 25% w/w aqueous dispersion containing ethyl cellulose, ammonium hydroxide, medium chain triglycerides & Oleic acid with a pH of about 9.5-11.5 0.5% to 25%, Citric acid 0.3%, Sorbitol (powder) 5% to 70%, Maltodextrin 1% to 50%, Sodium Bicarbonate 0.25-% to 10%, licorice extract as ammonia salt of Glycyrrhizic Acid 0.1% to 10%, and pharmaceutically permissible flavors 0.25% to 5%.

12. A method of preparing an unpleasant-taste-masked pharmaceutical composition of claim 3 comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener; wherein:

a. the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener,
b. the agglomerate comprises a coating of a water insoluble material on the same wherein the thickness of the coating is strong enough to prevent immediate release of unpleasant taste on tongue when orally administered but releases more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus,

c. the method comprising steps of:

i. dissolving the pharmaceutically active compound in a volatile organic solvent,

ii. dissolving a low intensity sweetener and a high intensity sweetener in water,

iii. transferring composition of Step i. and ii. into a vacuum dryer and to get dry agglomerate,

iv. milling and sifting the dry agglomerate,

v. coating the agglomerate with a water insoluble material to get taste masked agglomerate granules,

vi. mixing the agglomerate granules of step v. with excipients or/and adjuvants,

vii. and optionally filling in sachets.

13. The method of claim 12 comprising steps of:

i. dissolving Acetaminophen in Isopropyl alcohol,

ii. dissolving Mannitol and Sucralose in Purified water,
iii. transferring the composition of Step 1 and 2 into a vacuum dryer and drying to get agglomerate till the moisture content is less than 2%,

iv. after drying, unloading, milling and sifting through 40 mesh sieve to get agglomerate granules,

v. coating the 40 mesh agglomerate granules of step no. iv. with an aqueous coating system utilizing Ethylcellulose as the polymer, and sifting the coated material through 40 mesh sieve to get uniformly sized taste masked agglomerate granules,

vi. adding excipient/adjuvents, and flavors,

vii. sifting the materials through 40 mesh and blending along with taste masked agglomerate granules in a blender, and

viii. optionally filling in to sachets.

14. The unpleasant-taste-masked pharmaceutical composition of claim 4 comprising, as percentage of the composition, Acetaminophen 10 to 90 %, Sodium carboxymethylcellulose 5 to 50%, Sucralose 0.1 to 5 %, Cellulose acetate 0.5 to 10 %, sodium chloride 0.1 to 2.0 %, Mannitol 5 to 90 %, Xylitol 5 to 60%, Sorbitol 5 to 70%, Magnesium Stearate 0.5 to 5.0%, pharmaceutically permissible flavors 0.1 to 5% Licorice extract as ammonia salt of Glycyrrhizic Acid 0.1 to 10 %.

15. A method of making unpleasant-taste-masked pharmaceutical composition of claim 4 comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an
agglomerate of the pharmaceutically active compounds and at least one sweetener; wherein:

a. the sweetener in the agglomerate comprises at least a high intensity sweetener, or a mixture of one or more of low intensity sweetener and at least one high intensity sweetener,

b. the agglomerate further comprising a hydrophilic thickener incorporated in the agglomerate,
c. the agglomerate is coated with a water insoluble material on the agglomerate wherein the thickness of the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus;

d. the method comprising steps of:
i. making gel mass of a thickener in water,
ii. adding the pharmaceutically active compound to the gel mass,
iii. adding high intensity sweetener to the gel mass of the thickener,
iv. drying the gel mass to get dry agglomerate,
v. milling and sifting the agglomerate through sieve,
vi. dissolving water insoluble material in one or a mixture of volatile organic solvent/s and coating the dried agglomerate
with a coat of a water insoluble material such that the coating is strong enough to prevent release of unpleasant taste on tongue when orally administered but release more than 80% of the pharmaceutically active unpleasant tasting compound in 15 minutes when subjected to dissolution in Phosphate buffer pH 5.8 media using USP Type 2 apparatus,

vii. optionally adding excipients, and

viii. optionally filling the powder in sachets.

16. The method of claim 15 comprising steps of:

i. heating water to about 60° C and adding sodium carboxymethylcellulose slowly under stirring to get a gel mass,

ii. adding Acetaminophen to the above under stirring,

iii. dissolving Sucralose in water and adding to the above under stirring,

iv. unloading the gel mass and drying in tray drier/vacuum drier till the Loss on drying (LOD) is less than 4% to get a dry agglomerate,

v. sifting the dried material through a # 40 sieve,

vi. preparing coating solution by dissolving Cellulose acetate in Isopropyl alcohol and Dichloromethane,

vii. coating the dried and sifted agglomerate of step no. v. with coating solution of step no. 6, allowing the organic solvent to
evaporate and sifting the dried coated agglomerate through #
40 sieve,
viii. optionally adding excipients, sifting through # 40 sieve and
blending along with the above granules in a blender, and
 ix. optionally filling the powder in sachets.
17. The unpleasant-taste-masked pharmaceutical composition of claim 5
comprising, as percentage of the composition, Acetaminophen 10 to 90 %,
Mannitol 5 to 90 %, sucralose 0.1 to 5 %, Polyvinylpyrrolidone with K value
30 0.25 to 5 %, Titanium dioxide 0.25 to 5 %, pharmaceutically permissible
color 0.01 to 2 %, Maltodextrin 5 to 50 %, sodium benzoate 0.1 to 2 % and
pharmaceutically permissible flavor 0.1 to 5 %.
18. A method of making an unpleasant-taste-masked pharmaceutical composition
of claim 5 comprising at least one pharmaceutical active compound of
unpleasant taste; the said pharmaceutical composition comprising an
agglomerate of the pharmaceutically active compound/s and at least one
sweetener, wherein:
   a. the sweetener in the agglomerate comprises at least a high intensity
sweetener, or a mixture of one or more of low intensity sweetener and
at least one high intensity sweetener,
   b. further comprising at least one binding polymer in the agglomerate;
   c. the method comprising following steps of:
      i. dissolving the pharmaceutically active compound in a volatile
organic solvent,
ii. dissolving a low intensity sweetener and high intensity sweetener in water,

iii. transferring composition of step i. and step ii. into a vacuum dryer and drying into an agglomerate having moisture content less than 2%,

iv. after drying, milling and sifting the agglomerate and mixing with colorants,

v. granulating the above dried agglomerate with binding solution prepared with a water insoluble binding agent,

vi. blending the dried agglomerate granules with fillers and excipients,

vii. optionally filling the blend in sachets.

19. The method of claim 18 comprising steps of:

a. dissolving Acetaminophen in Isopropyl alcohol,

b. dissolving Mannitol and Sucralose in water,

c. transferring compositions of Step a and b into a vacuum dryer and drying till the loss on drying (LOD) of the resulting agglomerate is less than 2%,

d. milling and sifting the agglomerate through # 40 sieve and mixing with pharmaceutically acceptable colorants selected from the group titanium dioxide and Sunset Yellow FCF,

e. granulating the above agglomerate with binding solution prepared with Polyvinylpyrrolidone with K value 30, and purified water in a granulator and drying in a drier to produce agglomerate granules,
f. sifting the dried agglomerate granules through #40 sieve and loading into a blender,
g. adding #40 sieve sifted Maltodextrin, Sodium Benzoate and Orange juice flavor Permaseal (PHS 133147) into the same above blender and mixing for 15 minutes,
h. optionally filling the powder in Sachets.

20. The unpleasant-taste-masked pharmaceutical composition of claim 6 comprising, as percentage of the composition: acetaminophen 10 to 90%, Mannitol 5 to 90%, Sucralose 0.1 to 5%, Citric acid 0.25 to 10%, Sodium bicarbonate 1 to 30%, Sorbitol powder 5 to 70%, Maltodextrin 5 to 50%, Licorice extract as ammonia salt of Glycyrrhizic Acid 0.1 to 10% and Pharmaceutically permissible flavor 0.1 to 5%.

21. A method of making an unpleasant-taste-masked pharmaceutical composition of claim 6 comprising at least one pharmaceutical active compound of unpleasant taste; the said pharmaceutical composition comprising an agglomerate of the pharmaceutically active compound/s and at least one sweetener, further comprising effervescence generating means; the method comprising steps of:
   a. dissolving the pharmaceutically active compound in a volatile organic solvent and transferring into a vacuum dryer,
   b. adding and dissolving a food acid and an alkali capable of producing effervescence when contacted with water,
   c. dissolving a high intensity sweetener and a low intensity sweetener into the above organic solvent containing the ingredients added above
and drying the whole composition in the vacuum dryer to get an agglomerate,
d. sifting the dried agglomerate through a mesh,
e. adding fillers and excipients to the agglomerate, mixing well,
f. optionally filling the above blended powder into sachets.

22. A method of claim 21 comprising steps of:
   a. dissolving Acetaminophen in Ethanol and transferring into a vacuum dryer,
   b. adding Citric acid to the above and stirring to get clear solution,
   c. adding Sodium bicarbonate to it and mixing for 15-20 minutes,
   d. transferring Sucralose and Mannitol into the above vacuum dryer and drying till the loss on drying is less than 2% in the resulting agglomerate,
   e. sifting the dried agglomerate through #40sieve,
   f. sifting Maltodextrin, Sorbitol powder, Magna sweet, and Strawberry flavour through #40 sieve blending and mixing for 15 minutes,
   g. optionally filling into sachets.
### A. CLASSIFICATION OF SUBJECT MATTER
**INV. A61K9/16**

**ADD.**

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**A61K**

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

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>claims 1-27</td>
<td>1-22</td>
</tr>
<tr>
<td>X</td>
<td>WO 99/32092 A1 (SMITHKLINE BEECHAM CORP [US]; VENKATESH GOPADI M [US]; PALEPU NAGESWAR) 1 July 1999 (1999-07-01)</td>
<td>1,2,5</td>
</tr>
<tr>
<td>Y</td>
<td>examples</td>
<td>1-22</td>
</tr>
<tr>
<td>X</td>
<td>WO 01/39749 A2 (PANACEA BIOTEC LTD [IN]; SINGH AMARJIT [IN]; JAIN RAJESH [IN]) 7 June 2001 (2001-06-07)</td>
<td>1,5</td>
</tr>
<tr>
<td>Y</td>
<td>page 35, paragraphs 2, 4</td>
<td>1-22</td>
</tr>
</tbody>
</table>

- **X** Further documents are listed in the continuation of Box C.
- **X** See patent family annex.

**"A"** document defining the general state of the art which is not considered to be of particular relevance

**"E"** earlier application or patent but published on or after the international filing date

**"L"** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

**"O"** document referring to an oral disclosure, use, exhibition or other means

**"P"** document published prior to the international filing date but later than the priority date claimed

**"T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**"Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**"A"** document member of the same patent family

<table>
<thead>
<tr>
<th>Date of the actual completion of the international search</th>
<th>Date of mailing of the international search report</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 October 2013</td>
<td>22/10/2013</td>
</tr>
</tbody>
</table>

**Name and mailing address of the ISA/Office**

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

**Authorized officer**

Schule, Stefanie
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 03/053415 AI (ELAN PHARMA INT LTD [IE]; STROPOLO FEDERICO [CH]; CCARELLO FRANCO []) 3 July 2003 (2003-07-03)</td>
<td>1, 2, 4, 5</td>
</tr>
<tr>
<td>Y</td>
<td>Example 19</td>
<td>1-22</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>WO 2007074472 A2</td>
<td>05-07-2007</td>
<td>BR P10620578 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1978939 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009521523 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008317853 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2007074472 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200805606 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1931999 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2002300238 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9813808 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2315088 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1284867 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO 4990940 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1047407 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0100469 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 136831 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2001526212 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO 20003150 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 505123 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 341353 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TR 200001856 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 586943 B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6475510 B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9932092 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 9811630 A</td>
</tr>
<tr>
<td>WO 0139749 A2</td>
<td>07-06-2001</td>
<td>AU 3221401 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0015994 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 20021855 A3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1235561 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2216319 CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UA 78485 C2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 7122198 B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 0139749 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200204193 A</td>
</tr>
<tr>
<td>WO 03053415 A1</td>
<td>03-07-2003</td>
<td>AT 333270 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2470859 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60213283 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1463488 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2005118258 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 03053415 A1</td>
</tr>
</tbody>
</table>