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/adjuncts 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 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 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.
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 and 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 orodispersible 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, Phenylpropanolamine, cephalixin, Midazolam, Clindamycin, Omeprazole, Dexamethasone, Phenobarbital, Dicloxacillin Prednisolone, Furosemide, Prednisone, Iron Sulfate Metronidazole, Metoclopramide HCl, Ofloxacin, Norfloxacain, Fluconazole, Azithromycin, Clarithromycin, Roxithromycin, Tramadol, Folic Acid, Anticholesterolemic saponins, Levofloxacin, Ciprofloxacin, Sildenafil citrate, Dextromethorphan hydrobromide, Ampicillin trihydrate, Nizatidine, Roxithromycin, Clarithromycin, Chloroquine diphosphphate, 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 Maltodextrin, Sodium Benzoate, Sodium Chloride, Mannitol, Xylitol, Citric acid, Sorbitol powder, Sucralose, other sweeteners Magnasweet, Sodium bicarbonate, Magnesium Stearate and flavors,

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, Glyceryl dibehenate, Polyethylene glycols, Glyceryl dipalmitostearate, Propylene glycol monocaprylate, Glyceryl 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, galactocaroleose, pectin, amylose, pullulan, glycogen, amylopectin, 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 of claim 2 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

Macrocristalline 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 4%,
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 9.5-1.5 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 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.

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 at least one 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 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 #40 sieve,
f. sifting Maltodextrin, Sorbitol powder, Magna sweet, and Strawberry flavour through #40 sieve blending and mixing for 15 minutes,
g. optionally filling into sachets.
STATEMENT UNDER ARTICLE 19 (1)

The applicant respectfully submits his response to Box no. V in the Written Opinion of the International Searching Authority.

Claim 1 is amended to shift the semicolon after the word "compound/s" to a location after the phrase "at least one sweetener" and inserting the word "and" behind the phrase "at least one sweetener". This is fully supported by the "as filed" specification throughout the specification, including page 5 lines 1-3 which categorically states that "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." Page 6 line 5 to 12 also specifically state that the pharmaceutical composition of the instant invention comprises an agglomerate of the pharmaceutically active compound/s and at least one sweetener; 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. This has been supported also by claims 9, 12, 15, 18 and 20 of the "as filed" claims.

Claim 7(d) is amended to insert "Maltodextrin, Sodium Benzoate, Sodium Chloride, Mannitol, other sweeteners and flavors". This insertion is supported by lines 24 page 12 to line 2 page 13, line 9 to line 11 page 14, line 7 to 8 page 15, line 4 to 5 page 16 of the "as filed" patent application, In claim 7(i) the "M" of Maltodextrin is capitalized, which is a grammatical error, hence the amendment is allowable.

The claim 9 is amended to delete the phrase "a pharmaceutical composition" which is an obvious meaningless repetition of the same phrase in the same claim.
and is an editing mistake. Its deletion does not change the scope of the claim 9 in any way. Hence, it is submitted that, the deletion is an allowable amendment. Claim 10(c) is amended to delete "2" and replace it by "4". This is supported by line 23 of page 6 of the "as filed" patent application.

In claim 20, "A" of Acetaminophen is capitalized, which is an allowable grammatical amendment.

In claim 21(b), "and dissolving" is deleted. This is deletion of an obvious technical error, since it is clear that "a food acid and an alkali capable of producing effervescence when contacted with water" cannot dissolve in a volatile organic solvent. Being an obvious technical error, the amendment is allowable.

Thus, no new matter has been added.

There may be a need to amend the description.