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(54) Title: TABLET COMPOSITION

(57) Abstract

A tablet composition is disclosed, comprising: (a) a drug active; (b) a thickening agent; and (c) a sugar agent, wherein the composition is in solid form, and wherein the ratio of the thickening agent to the sugar agent causes the composition to become a paste when contacted with saliva.

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# TABLET COMPOSITION

## FIELD

The present invention relates to a tablet composition comprising a drug active.

## BACKGROUND

Orally administered compositions are given to the patient in many forms, such as liquid solutions including gels, emulsions, and suspensions; or in solid forms such as powders, granules, and tablets. Compositions administered in solid form, especially tablets, are usually intended to be swallowed whole or chewed.

Many consumers, particularly those who have difficulty swallowing a tablet (*e.g.*, the aged or children), prefer tablets which can be readily ingested by chewing. Such people desire tablets which dissolve immediately during chewing in the mouth.

However, conventional tablets tend to produce an unacceptable mouthfeel (*i.e.*, overall sensation of the product in the mouth) for the user. Product attributes which tend to contribute to an unacceptable mouthfeel include bitterness (typically caused by the drug active contained in the table) and grittiness (*i.e.*, the textural aspects of the granules making up the tablet, as sensed by the tongue and/or upper palate). Such unacceptable mouthfeel properties tend to make the tablet (in chewed or unchewed form) difficult for the user to swallow.

Some of active ingredients which tend to exhibit the undesirable characteristic of bitter taste after oral administration by *e.g.*, swallowing and/or chewing, include *e.g.*, acetaminophen, ampicillin, azithromycin, chlorpheniramine, cimetidine, dextromethorphan, diphenhydramine, erythromycin, ibuprofen, penicillin, phenylbutazone, psuedoephedrine, ranitidine, spironolactone, and theophylline for pharmaceutical compositions. See Keating

U.S. Patent 2,990,332, Koff U.S. Patent 3,138,525, Raghunathan U.S. Patent 4,221,778, and Kelleher U.S. Patent 4,996,047.

Various formulation approaches for have been taken to address the issues of bitterness and/or grittiness For example, U.S. Patent 3,138,525 (Koff, issued June 23, 1964); U.S. Patent 4,221,778 (Raghunathan, September 9, 1980); and U.S. Patent 4,996,047 (Kelleher et al, February 26, 1991).

Based on the foregoing, there is a need for a drug delivery tablet composition which has improved mouthfeel properties and/or is easier for the user to swallow.

## SUMMARY

The present invention is directed to a composition comprising a drug active; a thickening agent; and a sugar agent; wherein the composition is in solid form, and wherein the ratio of the thickening agent to the sugar agent causes the composition to become a paste when contacted with saliva.

These and other features, aspects, and advantages of the present invention will become better understood from a reading of the following description, and appended claims.

## DETAILED DESCRIPTION

While the specification concludes with claims particularly pointing out and distinctly claiming the invention, it is believed that the present invention will be better understood from the following description.

All percentages and ratios used hereinafter are by weight of total composition, unless otherwise indicated.

All measurements referred to herein are made at 25°C unless otherwise specified.

All percentages, ratios, and levels of ingredients referred to herein are based on the actual amount of the ingredient, and do not include solvents, fillers, or other materials with which the ingredient may be combined as a commercially available product, unless otherwise indicated.

All publications, patent applications, and issued patents mentioned herein are hereby incorporated in their entirety by reference. Citation of any reference is not an admission regarding any determination as to its availability as prior art to the claimed invention.

Herein, "comprising" means that other steps and other components which do not affect the end result can be added. This term encompasses the terms "consisting of" and "consisting essentially of."

Herein, "solid tablet" means a material which has a hard shape and is made by compressing granules pre-mixed into a predetermined shape or direct compression of ingredients contained, which includes, *e.g.*, pills, lozenges, and troches.

Herein, "paste" means a material which is in smooth liquid form having higher or lower viscosity, *e.g.*, gel form and cream form.

The present invention relates to a composition comprising a drug active; a thickening agent; and a sugar agent; wherein the composition is in solid form, and wherein the ratio of the thickening agent to the sugar agent causes the composition to become a paste when contacted with saliva. It is believed that tablets, when wetted with water, start penetration of water, swelling its structure, dissolving and destroying its shape, thereby the tablets change the structure into paste.

The aspects and embodiments at the present invention set forth in this document have many advantages, including improved mouthfeel and/or improved dissolution in the mouth. For example, in one aspect of the present invention, the tablet composition converts into a paste when contacted with saliva in the mouth. Such a paste facilitates the user's swallowing the composition. In another aspect of the present invention, the paste provides an improved mouthfeel by, *e.g.*, masking the bitter taste otherwise produced by the drug active and/or reducing any gritty sensation otherwise experienced by the user.

In a preferred embodiment, the ratio of the thickening agent to the sugar agent included in the composition is at least about 1:7. Such a ratio is believed to facilitate maintaining separation of individual particles of the thickening agent, (*i.e.*, preventing their lumping together) when the composition is contacted with saliva in the mouth.

In yet another aspect of the present invention, the paste of the composition prevents the user from experiencing the bitter taste of the drug active. Without being bound by theory, it is believed the combination of the thickening agent and sugar agent "suspends" the drug active in the paste form, such that the drug active does not fully contact the bitter sensing taste buds of the mouth. While conventional formulations have, in some cases, resorted to

coating the drug active (*e.g.*, drug resin complex) to prevent such a bitter taste sensation, such a formulation step is not necessary in the composition of the present invention. For example, an embodiment of the present invention comprising an uncoated drug resin complex would also result in little or no bitter taste sensation to user.

In another aspect at the present invention, the composition can contain a higher concentration of drug actives in comparison with those included in the conventional tablets or lozenges. For example, the composition could contain from about 2 to about 6 times or more of an uncoated drug resin active, versus conventional compositions containing an uncoated resin composition.

A. Drug active

The composition of the present invention includes a drug active. Herein, "drug active" refers to an ingredient intended to be delivered (*e.g.*, ingested by) the user for therapeutic treatment. Preferably the drug active is a drug resin complex. The drug resin complex contains an active ingredient which is conventionally used in pharmaceutical industries, in combination with an ionic exchange resin (*e.g.*, cation), thereby delaying the release of the active ingredients during administration, for example, until the composition reaches the gastrointestinal tract.

Exemplary active ingredients which are suitable for the use in the drug resin complex may be acidic, basic or amphoteric. Examples of acidic drugs useful herein include, but are not limited to, dehydrocholic acid, diflunisal, ethacrynic acid, fenoprofen, furosemide, gemfibrozil, ibuprofen, naproxen, phenytoin, probenecid, sulindac, theophylline, salicylic acid and acetylsalicylic acid.

Exemplary active ingredients which are basic include, but are not limited to, acetophenazine, amitriptyline, amphetamine, benztropine, biperiden, bromodiphenhydramine, brompheniramine, carbinoxamine, chlorcyclizine, chlorpheniramine, chlorphenoxamine, chlorpromazine, clemastine, clomiphene, clonidine, codeine, cyclizine, cyclobenzaprine, cyproheptadine, desipramine, dexbrompheniramine, dexchlorpheniramine, dextroamphetamine, dextromethorphan, dicyclomine, diphemanil, diphenhydramine, doxepin, doxylamine, ergotamine, fluphenazine, haloperidol, hydrocodone, hydroxychloroquine, hydroxyzine, hyoscyamine, imipramine, levopropoxyphene,

maprotiline, meclizine, mepenzolate, meperidine, mephentermine, mesoridazine, methadone, methdilazine, methscopolamine, methysergide, metoprolol, nortriptylene, noscapine, nylindrin, orphenadrine, papaverine, pentazocine, phendimetrazine, phentermine, phenylpropanolamine, pyrilamine, tripelennamine, triprolidine, promazine, propoxyphene, propanolol, pseudoephedrine, quinidine, and scopolamine.

Exemplary amphoteric drugs useful herein include, but are not limited to, aminocaproic acid, aminosalicylic acid, hydromorphone, isoxsuprine, levorphanol, melphalan, morphine, nalidixic acid, and paraaminosalicylic acid.

Preferred ion-exchange resins (hereinafter, "ion-exchanger") useful herein are water-insoluble resins and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate pH conditions. The organic matrix may be synthetic (*e.g.*, polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (*e.g.*, modified cellulose and dextrans).

The inorganic matrix can also be, *e.g.*, silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (*e.g.*, sulfonic acid), weakly acidic (*e.g.*, carboxylic acid), strongly basic (*e.g.*, quaternary ammonium), weakly basic (*e.g.*, primary amine), or a combination of acidic and basic groups. In general, those types of ion-exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are suitable for use in the compositions of the invention.

Examples of such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp. 344-361) in Chromatoqraohy. (E. Heftmann, editor), Van Nostrand Reinhold Company, New York (1975).

Preferably, the particle size of the ion-exchangers is from about 40 microns to about 150 microns. Particle sizes substantially below the lower limit tend to be difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit (*e.g.*, commercially available ion-exchange resins having a spherical shape and diameters up to about 1000 microns) tend to be gritty in solid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Binding of drug ingredients and resins can be accomplished by any of the methods known in the art, the selection depending upon the drug ingredient and the ion-exchanger making up the desired drug resin complex. The concentration of the drug ingredient and the resin can be also selected depending upon the characteristic of the resultant drug resin complex necessary to meet the requirement of the therapy.

The drug resin complex useful herein can be uncoated or coated. Preferably the coating material comprises water permeable diffusion components. In a preferred embodiment, the drug active (*e.g.*, drug resin complex) is uncoated.

The drug resin complex preferably has an uncoated particle size of from about 10 microns to about 150 microns. In coated drug active embodiments, such a size range will increase, commensurate with the thickness of the coating. It is believed a higher particle size of drug resin complex may lead to an unacceptable gritty mouthfeel when the tablet is converted into the paste form in the mouth. The lower particle size tends to provide manufacturing loss and result in difficulty of handling during processing.

In a preferred embodiment, the drug active useful herein is present at a level of from about 0.5 to about 16.0 %, preferably from about 1.0 to about 12.0%. These levels of drug resin complex without coating are up to 6 times compared to those included in the conventional tablets.

B. Thickening agent

The composition of the present invention also includes a thickening agent. Herein, "thickening agent" refers to a material which provides a desirable consistency when contacted with saliva and/or water in the mouth. Such thickening agents in the composition have characteristics such as wetting quickly and absorbing fluid when contacted with water and/or saliva, thereby swelling and converting into a paste. It is believed that water is absorbed into the structure of the composition maintaining cohesiveness of the composition structure. When more and more water enters the composition structure, more swelling takes place and a paste is formed.

Nonlimiting examples of thickening agents useful herein include: pregelatinized starch; gums such as agars, locust bean gums, guar gums, and tara gums; carrageenan; alginate; xanthan; dextran; and cellulose derivatives

such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Synthetic silicates such as colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. The thickening agent is preferably present from about 0.2% to about 5.5% by weight of the composition.

C. Sugar agent

The composition of the present invention also includes a sugar agent. Herein, "sugar agent" refers to a material which is used to enhance salivation and help in dissolution of the composition. The sugar agent presents in the composition can provide sweetness to the formulation, and a desirable dissolution property to the composition as well as aid in the processing of the composition into tablet form. The sugar agent is believed to keep the individual particles of the thickening agent separated and prevent their lumping when contacted with saliva and/or water.

Preferably, the sugar agent useful herein is a sugar, sugar alcohol, or mixture thereof. Nonlimiting examples of sugars useful herein include lactose, glucose, maltodextrins, and sucrose. Sugar alcohols useful herein include sorbitol, xylitol, mannitol and maltitol.

The total amount of sugar agent is selected depending upon its compatibility with the other ingredients, especially drug actives, and the desired characteristic of the composition such as dissolution and mouthfeel, *e.g.*, bitterness and grittiness of the tablet. The sugar agent is present at an effective level, preferably at a level of from about 20% to about 80%, more preferably from about 20% to about 65% by weight.

Preferably, the sugar agent of the present invention is a combination of sugar and sugar alcohol, more preferably the ratio of sugar of such combination is lower than the ratio of sugar alcohol. A preferred combination is sucrose (sugar) with a higher ratio of mannitol (sugar alcohol). It is believed the combination of sugar and sugar alcohol as the sugar agent improves the pleasant dissolution provided by the combination of the sugar agent with thickening agent. Inclusion of mannitol slows the dissolution speed of the composition as compared to inclusion of sugar only. Without being bound by theory, it is believed that dissolution of a sugar agent having a faster dissolving

speed may cause the formation of a thick film around the individual particles of thickening agents, undissolved sugar agents, and other particles included in the composition. Such a thick film tends to prevent further penetration of water into the composition structures and particles which have not dissolved yet; thereby preventing complete and/or even dissolution of the composition as a whole.

Preferably, the composition includes from about 1.0 to about 50% of sugar and from about 20 to about 80% of sugar alcohol by weight of the composition.

In one embodiment, the sugar agent may further include a binding agent. Inclusion of the binding agent is particularly useful when a sugar agent, such as mannitol, may have a limited ability to bind the components used for the composition. It is believed that insufficiencies in binding ability tend to cause tablets to break off, *e.g.*, into two pieces along the length of the tablet during the manufacturing process. This splitting of the tablet is commonly referred to as "capping." The levels and types of binding agent are selected depending upon the character of the carriers, compatibility with other components, and desired characteristic of the final product.

In addition, when the composition is in tablet form, it is recognized that some sugar agent of the present invention may also have properties as a binding agent for making tablets. Most of the sugar agents herein, preferably sugar, may be useful for providing improved binding properties of the composition in tablet form to prevent the tablet from breaking into two pieces.

Examples of useful binding agents, other than the previously described sugar agents, include starches such as starch paste and pregelatinized starch; polyvinylpyrrolidone; cellulose derivatives; gelatin; gums; and mixtures thereof. In certain embodiments, the binding agent and the tableting carrier may be made of the same material. Alternatively, the binding agent and the sugar agent may be altogether different. The binding agent is present in an effective amount, preferably from about 0.1% to about 5% by weight, more preferably from about 0.5% to about 3%.

D. Water insoluble diluent

The composition of the present invention can further include a water insoluble diluent. Herein, "water insoluble diluent" means a material which improves the disintegration or dispersion property of the tablet composition. Without being bound by theory, it is believed that the water insoluble diluent

tends to provide a desired porosity to the composition. Such porosity is believed to provide channels for water into the tablet structure, thereby allowing penetration of, and more exposure of the composition surface area to, the water. The water insoluble diluent useful herein is any material which is insoluble in water which improves the dissolution of the composition, versus a composition that does not contain the material. The water insoluble diluent useful herein includes, but is not limited to, calcium carbonate, calcium phosphate, and the like. Preferably, the water insoluble diluent is present at an effective level, preferably at a level of from about 0.5% to about 70% of the tablet composition.

E. Tableting carrier

The composition of the present invention can further include a tableting carrier. Herein, "tableting carrier" means one or more compatible solid or liquid substances, preferably in solid form, which are suitable for oral administration to a human and commonly used for making tablets. The tableting carrier must be of sufficiently high purity and sufficiently low toxicity to render the tablet suitable for administration to human beings. Examples of useful tableting carriers include the water insoluble diluent, a tableting aid, a coloring agent, a flavoring agent, the granulating fluid, and mixtures thereof. Preferably, the tableting carrier is present from about 10 to about 80%, more preferably from about 30 to about 80% by weight.

1. Tableting aid

Herein, "tableting aid" refers to an ingredient that is added in small quantities to the composition to provide flowability during manufacturing, to reduce friction, and/or to ease removal of the tablets from the tableting machine. The tableting aids useful herein include, for example, magnesium stearate, stearic acid, aerosol, talc, and mixtures thereof. Preferably, the tableting aid is present in an amount sufficient to prevent the tablet from breaking into two pieces, preferably from about 2% to about 8%, by weight.

2. Coloring agent

The tablet composition of the present invention may further include a coloring agent. Preferably, the coloring agent is added with the granulating fluid to facilitate uniform distribution and mixing. The coloring agent is present at an effective level, preferably from about 10ppm to about 500ppm, more preferably from about 20ppm to about 250ppm by weight.

3. Flavoring agent

Flavoring agents may also be added to the tablet composition of the present invention. Examples of flavoring agents useful herein include oil of peppermint, oil of sassafras, clove bud oil, peppermint, menthol, anethole, thymol, methyl salicylate, eucalyptol, cassia, 1-menthyl acetate, sage, eugenol, parsley oil, oxanone, oil of wintergreen, alpha-irisone, oil of spearmint, marjoram, lemon, orange, propenyl guaethol, cinnamon, and mixtures thereof. Flavoring agents are generally used in the tablet composition at levels of from about 0.01% to about 5% by weight.

The tablet composition in accordance with the present invention may further, optionally, include other known compounds having the capability to enhance substantivity of a sweetener, if desired. These compounds is added to increase the overall sweetness impact. Such compounds include, but are not limited to, saccharine, aspartame, acesulfame K, and glycyrrhizin.

F. Method for making tablets

The composition of the present invention in tablet form can be produced by any method useful for forming conventional tablets known in the art. These conventional methods include granulating methods: either wet or dry granulating method, preferably wet granulating. Depending on the properties of the ingredients (*e.g.*, drug resin complexes, thickening agents, pharmaceutical acceptable carriers, flavors, coloring agents, and the like) to be formulated into granules, one method may provide a more favorable end product over the other method. The wet granulation method is widely used and usually produces the most satisfactory results in tablets. See, for example, E.J. de Jong; "The preparation of microgranulates, an improved tableting technique," Pharmaceutical Weekblad, 104(23), pages 469-474, 1969 and E.J. de Jong, U.S. Patent 3,266,992.

Direct compression may also be chosen for the present composition, as long as producing non-gritty tablets does not cause capping. See, for example, Blaaze, T. Palermo, et al., U.S. Patent 3,384,546.

In one embodiment, a method for making a composition in tablets form of the present invention comprises: (1) adding drug actives, sugar agents and any of additional ingredients which are stable in the proceeding process (*e.g.*, coloring agent), if needed, to make granules; (2) passing the granules through

#10 mesh; (3) drying the sieved granules through conventional drying techniques; (4) sieving again the dried granules through #14 mesh; (5) mixing the granules of step (4) with a thickening agent and any additional ingredients (*e.g.*, sweetening agent, flavour, tableting aids); and (6) compressing the mixture of step (5) to form tablets by conventional method.

## EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

The components shown below can be prepared by any conventional method known in the art. Suitable methods and formulations are as follows:

Examples 1 -2

| Ingredient | %w/w | |
|---|---|---|
| | Ex. 1 | Ex. 2 |
| Pseudoephedrine-IRP 69 Complex *1 | 11.12 | - |
| Dextromethorphan-Dow XYS40010 Complex *2 | - | 3.32 |
| Mannitol | 37.29 | 70.20 |
| Sugar | 8.00 | 4.15 |
| Calcium Carbonate | 34.94 | - |
| dicalcium phosphate | - | 12.50 |
| Aspartame | 0.35 | 0.28 |
| Xanthan Gum | 1.25 | 0.10 |
| Carboxymethyl cellulose | 2.15 | 0.15 |
| Synthetic silicate | 0.20 | 4.60 |
| Magnesium stearate | 2.00 | 2.00 |
| Talc | 2.50 | 2.50 |
| Flavour | 0.19 | 0.19 |
| Color | 0.01 | 0.01 |

*1 Pseudoephedrine-IRP 69 Complex: a drug-resin complex containing 35.69%w/w pseudoephedrine without coating, supplied by Rohm & Haas

*2 Dextromethorphan-Dow XYS40010 Complex: drug -resin complex containing 56.2 %w/w of dextromethorphan without any coating, provided by HCRC-P&G, US

The tablet having Example 1 formulation is made by the method described in "Method for making tablets" section.

The tablet having Example 2 formulation is made by the method described in "Method for making tablets" section, except the drug actives are added at step 5 during mixing of the granules, rather than at step 1.

The embodiments disclosed and represented by the previous examples have many advantages. For example, they become a paste when contacted with saliva, and thereby provide a desirable dissolution property and a pleasant mouthfeel such as non-bitter taste.

It is understood that examples and embodiments described herein are for illustrative purpose only and that various modifications or changes in right thereof will be suggested to one skill the art and are to be included in the spirit and purview of this application and scope of the appended claims.

What is claimed is:

1. A composition comprising
   (a) a drug active;
   (b) a thickening agent; and
   (c) a sugar agent,

wherein the composition is in solid form, and wherein the ratio of the thickening agent to the sugar agent causes the composition to become a paste when contacted with saliva.

2. The composition of Claim 1 wherein the ratio of the thickening agent to the sugar agent is at least about 1 : 7.

3. The composition of Claim 1 wherein the composition is a chewable tablet.

4. The composition of Claim 3 wherein the composition further comprises a water insoluble diluent

5. The composition of Claim 4 wherein the sugar agent is sugar, sugar alcohol, or mixtures thereof; and the thickening agent is a pregelatinized starch, a gum, a cellulose derivative, or mixtures thereof.

6. The composition of Claim 4 wherein the drug active is an non-coating drug resin complex.

7. The composition of Claim 4 wherein the drug active is coated with a water permeable diffusion barrier is methylacrylate polymer.

8. A composition comprising:
   (a) from about 0.5 to about 16.0 % of a drug-resin complex;
   (b) from about 0.2 to about 5.5 % of a thickening agent; and
   (c) from about 20 to about 80 % of a sugar agent;

wherein the composition is in tablet form.

9. The composition of Claim 8 wherein the composition further comprises from about 10 to about 80% of a tableting carrier selected from the group consisting of a water insoluble diluent, a tableting aid, a coloring agent, a flavoring agent, and mixtures thereof.

10. The composition of Claim 9 wherein the composition comprises from about 0.5 to about 70 % of the water insoluble diluent.

# INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 97/24122

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/20 A61K47/48

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)
IPC 6 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,Y | EP 0 492 235 A (BASF CORP) 1 July 1992<br>see the whole document | 1-6,8-10 |
| X,Y | US 5 686 107 A (RATNARAJ SHEILA ET AL) 11 November 1997<br>see the whole document | 1-6,8-10 |
| X,Y | EP 0 471 967 A (MERCK PATENT GMBH) 26 February 1992<br>see the whole document | 1-6,8-10 |
| Y | US 5 262 167 A (VEGESNA RAJU V K ET AL) 16 November 1993<br>see the whole document | 1-5,8-10 |
| A | US 5 633 005 A (IMER FARUK) 27 May 1997<br>see the whole document | 1-5,8-10 |

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[X] Further documents are listed in the continuation of box C.

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