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(71) Applicant: **EFFRX PHARMACEUTICALS SA** [CH/CH]; Wolleraustrasse 41B, CH-8807 Freienbach (CH).

(72) Inventor: **HAYWARD, Marshall, A.**; 655 Carlene Drive, Bridgewater, NJ 08807 (US).

(74) Agent: **MAI, Peter**; Kreuzberger Ting 64, 65205 Wiesbaden (DE).

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(54) Title: EFFERVESCENT FORMULATIONS THAT DELIVER PARTICLES WHICH FLOAT IN THE STOMACH

(57) Abstract: A delayed-release pharmaceutical composition, comprising; an effervescent tablet, granule, or powder containing a first effervescing organic acid component and a first effervescing base component, wherein said tablet granule, or powder is completely solubilized in drinking water at 25 °C within 2 minutes without stirring; and an effective amount of active pharmaceutical ingredient (API) coated with a delayed- release effervescent floating delivery system containing a second effervescing base component, which system is buoyant, in gastric fluid and thus increases gastric retention time (GRT) in a patient

Title

Effervescent Formulations That Deliver Particles Which Float in the Stomach

Field of the Invention

Effervescent delayed release formulations.

Background of the Invention

Sustained- or delayed-release pharmaceutical compositions are well known and generally employ specialized coatings based on pH or water solubility effects, placed on the active pharmaceutical ingredient (API). It is also known that drug release rates can be delayed or controlled by delivering an API to the stomach in a floating drug delivery system having a bulk density less than gastric fluid, which system remains buoyant in the stomach for an extended period of time and increases the gastric retention time (GRT). Typically as such a system is floating on the gastric fluid the API is released slowly at the desired rate, and, after release of the drug, the residual system is emptied from the stomach resulting in better control of the fluctuations in plasma drug concentration. Floating drug delivery systems include gas-generating and non-effervescent systems. Delayed-release coatings that depend on pH or water solubility effects are sometimes combined with floating systems.

Non-effervescent floating systems typically contain cellulose derivatives like starch and a higher fatty alcohol or fatty acid glyceride, bilayer compressed capsules, multilayered flexible sheet-like medicament devices, hollow microspheres of acrylic resins, polystyrene floatable shells, single and multiple unit devices with floatation chambers and microporous compartments and buoyant controlled release powder formulations, or hydrogels that expand to hundreds of times their dehydrated form when immersed in water. Oral drug delivery formulations made from these gels swell rapidly in the stomach, causing medications to move more slowly from the stomach to the intestines and be absorbed more efficiently by the body.

Gas-generating systems typically use effervescent components such as sodium bicarbonate, citric acid and tartaric acid. The stoichiometric ratio of citric acid and sodium bicarbonate optimal for gas generation is 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The insoluble coating allows

permeation of water causing carbon dioxide to release and the beads to float in the stomach. Other approaches include the use of highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lacotes and polyvinyl pyrrolodone coats with hydroxypropyl methylcellulose, and floating systems based on ion exchange resin technology.

Prior to the present invention, one would not expect to combine an effervescent floating system with a conventional effervescent tablet formulation for dissolving in water before ingestion by the patient. That is because commercial effervescent tablets and granules contain relatively large amounts of the acid/base couple to promote rapid disintegration, so the large amount of acid would react to some extent with the effervescent compounds within the floating system before it reached the stomach.

Summary of the Invention

An object of the present invention is to provide a delayed-release pharmaceutical composition, comprising:

an effervescent tablet, granule, or powder containing a first effervescing organic acid component and a first effervescing base component, wherein said tablet, granule, or powder is completely solubilized in drinking water at 25 ℃ within 2 minutes without stirring; and

an effective amount of active pharmaceutical ingredient (API) coated with a delayed-release effervescent floating delivery system containing a second effervescing base component, which system is buoyant in gastric fluid and thus increases gastric retention time (GRT) in a patient.

Another object of the invention is to provide a method for manufacturing a delayed-release pharmaceutical composition, comprising:

preparing an effervescent tablet, granule, or powder containing a first effervescing organic acid component and a first effervescing base component, and

adding an effective amount of an active pharmaceutical ingredient (API) coated with a delayed-release effervescent floating delivery system which is buoyant in gastric fluid, thus increasing gastric retention time (GRT) in a patient,

wherein said tablet, granule, or powder is completely solubilized in drinking water at 25 ºC within 2 minutes without stirring.

Brief Description of the Figures

Fig. 1 is a diagram showing a preferred embodiment of the manufacturing process using a LabRAM acoustic mixer.

Detailed Description of the Invention

As part of the first or main effervescent system, an acid source selected from the group consisting of: citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid; an anhydride of said acids; an acid salt selected from the group consisting of sodium dihydrogen phosphate, disodium dihydrogen pyrophosphate and sodium acid sulfite and mixtures of the acids, anhydrides and acid salts.

As part of the first or main effervescent system, a carbonate source is selected from the group consisting of: sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, sodium sesquicarbonate, sodium glycine carbonate, and mixtures thereof.

The delayed release pharmaceutical compositions of the invention may contain a single API (e.g., metformin HCl), pharmaceutically acceptable salt, hydrate, solvate, polymorph, stereoisomer, ester, prodrug and complexe thereof; or optionally may be combined with another API (e.g., metformin hydrochloride mixed with a compound selected from the group consisting of GLIPIZIDE, GLYBURIDE, PIOGLITAZONE HYDROCHLORIDE, REPAGLINIDE, ROSIGLITAZONE MALEATE, SAXAGLIPTIN, and SITAGLIPTIN PHOSPHATE).

The delayed-release effervescent floating delivery system pharmaceutical composition(s) of the invention contains the API, 2 – 10 % by weight of a second effervescing base component (e.g., sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, sodium sesquicarbonate, sodium glycine carbonate, and mixtures thereof), and one or more coatings such as film coating, enteric coating, bioadhesive coating, diffusion coating, and other non-water-permeable coatings known in the art.

These coatings can be functional or non-functional. A functional coating helps slow the release of the active ingredient at the required site of action. In one example, the coating prevents the API from contacting the mouth or esophagus thereby masking its taste. In another example, the coating remains intact until reaching the small intestine (e.g., an enteric coating). Dissolution of a pharmaceutical composition in the mouth can be prevented with a layer or coating of hydrophilic polymers such as cellulose or gelatin. Eudragit® of various grades or other suitable polymers may be incorporated in coating compositions to release the API in the colon.

Coating agents include, but are not limited to, polysaccharides such as maltodextrin, alkyl celluloses such as methyl or ethyl cellulose, hydroxyalkylcelluloses (e.g. hydroxypropylcellulose or hydroxypropylmethylcelluloses); polyvinylpyrrolidone, acacia, corn, sucrose, gelatin, shellac, cellulose acetate pthalate, lipids, synthetic resins, acrylic polymers, polyvinyl alcohol (PVA), copolymers of vinylpyrrolidone and vinyl acetate (e.g. marketed under the brand name of Plasdone ® and polymers based on methacrylic acid such as those marketed under the brand name of Eudragit®.

Excipients can be included along with the film formers to obtain satisfactory coatings. These excipients can include plasticizers such as dibutyl phthalate, triethyl citrate, dibutyl sibacate, triacetine, polyethylene glycol (PEG) and the like, antitacking agents such as talc, stearic acid, magnesium stearate and colloidal silicon dioxide and the like, surfactants such as polysorbates and sodium lauryl sulphate, fillers such as talc, precipitated calcium carbonate, polishing agents such as beeswax, carnauba wax, synthetic chlorinated wax and opacifying agents such as titanium dioxide and the like. All these excipients can be used at levels well known to the persons skilled in the art.

Non-permeable coatings of insoluble polymers, e.g., cellulose acetate, ethylcellulose, can be used as enteric coatings for delayed/modified release by inclusion of soluble pore formers in the coating, e.g., PEG, PVA, sugars, salts, detergents, triethyl citrate, triacetin, etc.

The coating is a sustained release coating. The beads are retained in the stomach by floating them, which also controls the drug release rate. Ad added agent such as alginate or polyacrylate may be used to form a floating raft, which will trap the beads.

Coatings of polymers that are susceptible to enzymatic cleavage by colonic bacteria are a means of ensuring release to distal ileum and ascending colon. Materials such as calcium pectinate can be applied as coatings to composition and multiparticulates that disintegrate in the lower gastrointestinal tract, due to bacterial action. Calcium pectinate capsules for encapsulation of bioadhesive multiparticulates are also available.

Preferred sustained release materials are cellulosic and polyacrylic acid polymers (e.g. poltycarbophils or Eudragits). These components control diffusion of water during the time it takes for the patient to swallow the efferevecent beverage. Once in the stomach, the acid in gastric juice will react with the second effervescent base, e.g., bicarbonate.. When the bicarbonate reacts, gas bubbles form. The coating ideally "gels" and traps the bicarbonate inside, making the little beads float.

The slow release pharmaceutical compositions of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan and hot melt (extrusion) coating. Such methods are well known to those skilled in the art.

The preferred controlled-release coatings are applied to the API using non-aqueous systems to protect the second effervescing base component from water.

In a preferred coating method, the API core particles are mixed with 2 to 10 wt.% of an effervescing base component, such as a bicarbonate salt (e.g., sodium bicarbonate), nanosilica (optionally), an inert media such as sucrose or glass beads, and water insoluble polymer particles, to produce coated API core particles. The coated API core particles are then subjected to mechanical stress, elevated temperature or a combination thereof in order to deform the

coating into a continuous film. The coating sticks to the core API particle when it is "pressed in place" by a hard, inert media particle such as sucrose. After coating the sucrose is then removed.

Optionally the coating includes a combination of water soluble or swellable coating material particles so that the water soluble or swellable particles are imbedded within a water insoluble, deformable continuous polymer layer.

The API in the coated API core particles does not release immediately in the mouth and thus the particles can be taste masked in this manner, yet the API is released in a relatively short time from the coated pharmaceutical formulation once reaching the stomach. At that time the second effervescing base component can react with acid in the gastric juice to generate carbon dioxide, causing the API particle to float on the gastric fluid and thus delay release of the API.

Dry coating may be accomplished by any suitable device known to a skilled person. Suitable devices include, but not limited to Comil (U3 Quadro Comil of Quadro Pennsylvania, U.S.), LabRAM (Resodyne Minnesota, U.S.), Magnetically Assisted Impact Coater (MAIC, Aveka Minnesota, U.S.) and Fluid Energy Mill (FEM, Qualification Micronizer of Sturtevant Massachusetts U.S.) The FEM is able to simultaneously mill and dry coat the particles to achieve particle sizes that are equal to or less than 50% of the initial particle size if smaller particles are desired. Dry coating of the particles can be accomplished in a relatively short time using such equipment, for example, 100 grams of coated API core particles may be dry coated in 5 to 10 minutes using a LabRAM.

Advantages of the present invention include reproducibility of both the high rate of solubilization of the effervescent tablet itself and the slow rate of API release. The present system offers flexibility in terms of release profile, compatibility of the essential components, and high uniformity of coating. The present method of dry particle coating is simple to implement for a wide range of API's. Coating weight is relatively low while the rate of production output per time are high. The invention uses bicarbonates and acceptable salts as an essential coating material. From a temperature standpoint it is a cold coating process, which helps with excipients (no melting) and no calcination reaction *in situ*. Refrigeration is possible. The process is compatible with FRV100 components, and it can be used as part of related processes, e.g., one

can combine granulation with fluid bed coating plus labRAM, depending on needs and circumstances.

The water-insoluble polymer is in particle form, with a median particle size in a range of from 1 μm to 20 μm, from 5 μm to 12 μm or from 5-6 μm. The water insoluble polymer is deformable under mechanical stress, elevated temperature or a combination thereof and thus is selected to have a Young's modulus of not greater than 420 MPa, or not greater than 200 MPa, or not greater than 100 MPa, as measured at 20 °C. Alternatively, the deformability should be equivalent to a Young's modulus of not greater than 420 MPa or not greater than 200 MPa, or not greater than 100 MPa, as measured at 20 °C when measured at elevated or reduced temperatures actually used for processing. Thus, it is contemplated, for example, that elevated processing temperatures could be employed to soften the water insoluble polymer for deformation or that a combination of softening at elevated temperature and mechanical stress can be employed.

The water insoluble polymer may be selected from easily deformable micronized polymers. The water insoluble polymer may be selected from the group consisting of polyethylene, polypropylene, polytetrafluoroethylene, carnauba wax, castor wax, polyamide wax, and combinations thereof.

The water insoluble layer should allow a diffusivity of the API in the range of 0-20 x 10^{-12} m^2/s or more preferable 5-15 x 10^{-12} m^2/s. The coatings result in a significant delay or reduction in API release for the first two to four minutes of release in a dissolution test indicative of taste-release in the mouth, while permitting complete dissolution of the effervescent tablet.

The water soluble or swellable material is in particle form, with a median particle size in a range of from 0.5 μm to 20 μm, or in a range of from 1 μm to 10 μm. The water swellable material swells upon absorption of water and may be selected from typical disintegrants used in the pharmaceutical industry as additives for blends made for tableting. Exemplary water swellable materials include crospovidone, croscarmellose and sodium starch glycolate. Such materials, if

not soluble in water, must swell upon absorption of water such that their diameter can increase to 120-600% of their original diameter prior to water exposure, more preferably, 200-600%.

The water soluble material has a solubility of at least 50 mg/ml in water at neutral pH and 20 °C. The water soluble material should be readily soluble in water and have an intrinsic dissolution rate of 3-60 $\mu g/m^2 s$. Water soluble materials having higher intrinsic dissolution rates of 60-300 $\mu g/m^2 s$ may also be used but should first be coated with a hydrophobic silica layer in an amount of 100-300% surface coverage. Examples of water soluble materials include micronizable materials such as sugars such as sucrose, polyols such as mannitol and sorbitol, polyvinylpyrrolidone, ethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), lactose, and poly-(ethylene oxide) (PEO), polymethacrylates (Eudragit brand polymers), and combinations thereof. Hydrophilic polymers are a particularly useful class of materials that may be used.

The amount of water soluble or water swellable material employed in the mixing step is in a range of from 0.1 wt. % to 25 wt. %, or from 0.5 wt. % to 13 wt. % of the total weight of the API core particles and coating materials.

Particles coated with the water soluble or water swellable material may be optionally dry coated with hydrophobic silica to a SAC from 100% to 400% to slow the dissolution rate of the API. This option is especially beneficial for coating materials that dissolve and/or swell too quickly to mask the API's taste. Dry coating with hydrophobic silica may produce a poorly wetting but still soluble particle.

The silica particles used for dry coating include hydrophobic silica or hydrophobically treated silica. Examples include Aerosil R972 silica (Degussa), CAB-O-SIL EH-5 silica (Cabot), OX-50 silica (Degussa), COSMO55 (Catalyst & Chemical Ind. Co. Ltd (Japan)), P-500 hydrophilic silica (Catalyst & Chemical Ind. Co. Ltd (Japan)) and TS5 silica (Cabot). In some embodiments, more than one type of silica may be used in combination. For example, TS5 and Aerosil R972 may be used together to coat the API core particles.

The coatings also permit at least 90% of the release of the uncoated API core particles at 30 minutes or 60 minutes, as desired, in a standard USP dissolution test indicative of dissolution in the GI tract. Specifically, in the first two minutes, the release from the test sample consisting of coated particles is nearly arrested by the coating, with less than 0.1 % of drug dissolving in a dissolution test indicative of taste-release in the mouth, more preferably, less than 0.01 % of drug dissolving in a dissolution test indicative of taste-release in the mouth. Also, in some embodiments less than about 1 % of drug dissolves in a dissolution test indicative of taste-release in the mouth at four minutes, more preferably less than 0.5 %, as compared with the release from a test sample of uncoated drug particles of comparable size.

Example 1

A deformable polymer, polyethylene (PE) wax having a particle size of 5.5 μm is used to coat metformin hydrochloride. The polyethylene wax has a Young's Modulus of 200 MPa. The mixture contains 20 wt.5 sucrose media, 10 wt.% nanosilica, 5 wt.% sodium bicarbonate, and 10 wt. % metformin HCl. The powder blend is processed using an acoustic mixer as shown in Figure 1.

<u>Example 1</u>

A deformable polymer, polyethylene (PE) wax having a particle size of 5.5 μm is used to coat metformin hydrochloride. The polyethylene wax has a Young's Modulus of 200 MPa. The mixture contains 20 wt.% sucrose media, 10 wt.% nanosilica, 5 wt.% sodium bicarbonate, and 10 wt. % metformin HCl. The powder blend is processed using an acoustic mixer as shown in Figure 1.

<u>Example 2</u>

Metformin HCl particles (10 wt.%) with a volume averaged median particle size of 41 μm are coated with PE wax (median particle size 5.5 μm) as the hydrophobic polymer and various different polymers as the hydrophilic polymer at a loading of 96:4 (hydrophobic to hydrophilic). The hydrophilic polymer particles are HPC (9 μm), EC (17 μm), lactose (8 μm) dry coated with Aerosil R972, and lactose (18 μm) dry coated with Aerosil R972. The mixture contains 25 wt.% sucrose media, 10 wt.% sodium bicarbonate, The

coating formulations with different hydrophilic polymers are all capable of taste masking the metformin while still achieving controlled release.

Examples of combinations	Weights A/B	Dosages
Canigiaflozin/Metformin • Invokana®	100 mg/250 mg, 200 mg/500 mg, 300 mg/500 mg 50mg/850mg, 150mg/850mg, 50mg/1000mg, 150mg/1000mg	**Initial:** 100 mg/250 mg once or twice daily **Range:** up to 300/2000 mg **Dose:** Taken once or twice daily
Glyburide/Metformin • Glucovance® • various generics	1.25 mg/250 mg, 2.5 mg/500 mg, 5 mg/500 mg	**Initial:** 1.25 mg/250 mg once or twice daily **Range:** up to 20/2000 mg **Dose:** Taken once or twice daily
Glipizide/Metformin • Metaglip® • various generics	2.5 mg/250 mg (pink), 2.5mg/500 mg (white), 5mg/500 mg (pink) oval tablets	**Initial:** 2.5 mg/250 mg daily or 2.5mg/500 mg twice daily **Range:** up to 20/2000 mg **Dose:** Taken once or twice daily
Rosiglitazone/Metformin • Avandamet® • various generics	2 mg/500 mg (pale pink), 2 mg/1000 mg (yellow), 4 mg/500 mg (orange), 4 mg/1000 mg (pink) oval tablets	**Initial:** 2 mg/5000 mg once or twice daily **Range:** up to 8 mg/2000 mg **Dose:** Taken twice daily
Pioglitazone/Metformin • ActoPlus Met® • various generics	15 mg/500 mg, 15 mg/850 mg (white to off-white) oblong tablets	**Initial:** 15 mg/500 mg or 15 mg/850 mg once or twice daily **Range:** up to 45 mg/2550 mg Dosed once or twice daily
Pioglitazone/Glimepiride • Duetact®	30 mg/2 mg, 30 mg/4 mg (white to off-white) tablets	**Initial:** 30 mg/2 mg or 30 mg/4 mg once daily **Range:** max of one tablet daily **Dose:** Taken once daily

Rosiglitazone/Glimepiride • Avandryl® • various generics	4 mg/1 mg (yellow), 4 mg/2 mg (orange), 4 mg/4 mg (pink) rounded triangle tablets	**Initial:** 4 mg/1 mg or 4 mg/2 mg once daily **Range:** up to 8 mg/4 mg **Dose:** Taken once daily
Sitagliptin/Metformin • Janumet®	50 mg/500 mg (light pink), 50 mg/1000mg (red) oblong tablets	**Initial:** 50 mg/500 mg or 50 mg/1000 mg twice daily **Range:** up to 100 mg/2000 mg **Dose:** Taken twice daily
Repaglinide/Metformin • PrandiMet®	1 mg/500 mg (yellow), 2 mg/500 mg (pink) tablets	**Initial:** 1 mg/500 mg twice daily **Range:** 10 mg/2500 mg, Max per dose 4 mg/1000 mg **Dose:** Taken twice or three times daily
Pioglitazone/Metformin XR • ActoPlus Met XR®	15 mg/1000 mg, 30 mg/1000 mg (white to off-white) round tablets	**Initial:** 15 mg/1000 mg or 30 mg/1000 mg once daily **Range:** up to 45 mg/2000 mg **Dose:** Taken once daily
Saxagliptin/Metformin XR • Kombiglyze XR®	5 mg/500 mg (light brown to brown), 5 mg/1000 mg (pink), 2.5 mg/1000 mg (pale yellow to light yellow) capsule-shaped tablets	**Initial:** 5 mg/500 mg or 5 mg/1000 mg once daily **Range:** up to 5 mg / 2000 mg **Dose:** Taken once daily

For fixed dose combinations, although metformin is sometimes dosed once, and more often twice (and sometimes even three times) per day, some of these drugs used in combination (like Januvia, the DPP4 inhibitor sitagliptan, or like the SGLT2 inhibitor canigloflozin), are taken once per day. In such instances a cumulative daily dosing approach may is preferred. For example, if the desired dose were 500 mg of metformin twice per day and 100 mg canagiflozin once per day, one could provide a dose of 500 mg metformin plus 50 mg canagliflozin twice per day, which keeps the drug product and dosing regimen simple.

The foregoing examples have been presented for the purpose of illustration and description only. The scope of the invention is to be determined from the claims appended hereto.

Claims

1. A delayed-release pharmaceutical composition, comprising:

an effervescent tablet, granule, or powder containing a first effervescing organic acid component and a first effervescing base component, wherein said tablet, granule, or powder is completely solubilized in drinking water at 25 ℃ within 2 minutes without stirring; and

an effective amount of active pharmaceutical ingredient (API) coated with a delayed-release effervescent floating delivery system containing a second effervescing base component, which system is buoyant in gastric fluid and thus increases gastric retention time (GRT) in a patient.

2. The composition of claim 1, wherein the API is coated with polyethylene.
3. The composition of claim 1, wherein the API is metformin HCl.
4. The composition of claim 1, wherein the API is a combination of Caniglaflozin and Metformin
5. The composition of claim 1, wherein the API is a combination of Glipizide and Metformin.

6. A method for manufacturing a delayed-release pharmaceutical composition, comprising:

preparing an effervescent tablet, granule, or powder containing a first effervescing organic acid component and a first effervescing base component, and

adding an effective amount of an active pharmaceutical ingredient (API) coated with a delayed-release effervescent floating delivery system which is buoyant in gastric fluid, thus increasing gastric retention time (GRT) in a patient,

wherein said tablet, granule, or powder is completely solubilized in drinking water at 25 ℃ within 2 minutes without stirring.

7. The method of claim 6, wherein the API is coated with polyethylene.
8. The method of claim 6, wherein the API is metformin HCl.
9. The composition of claim 6, wherein the API is a combination of Caniglaflozin and Metformin.
10. The composition of claim 6, wherein the API is a combination of Glipizide and Metformin.