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[54] **METHOD OF ADMINISTERING AZITHROMYCIN**

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[58] **Field of Search** 514/29, 960; 536/7.2; 424/464, 465, 474, 480, 481

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Zithromax (Trademark of Pfizer, Inc.) Capsules Package Insert for azithromycin capsule dosage form sold commercially in U.S.

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[57] **ABSTRACT**

An oral dosage form of azithromycin which does not exhibit an adverse food effect; Specific azithromycin oral dosage forms including tablets, powders for oral suspensions and unit dose packets; Methods of treating microbial infections with the dosage forms; And therapeutic packages containing the dosage forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZITHROMYCIN

This invention relates to a dosage form of azithromycin, and also to a method of treating a microbial infection which involves administering azithromycin in the fed state to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.

In general, it is known that the absorption and bioavailability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gastrointestinal (GI) tract because, in general, the gastric residence time of a drug is usually significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important inasmuch as, when a drug exhibits an adverse food effect, there is risk associated with administering it to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug bioavailability, the following being a non-comprehensive listing:

(1) The particular dosage form can affect bioavailability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may vary depending on whether the subject has eaten or is fasted.

(2) The pH of the stomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected accordingly.

(3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal eaten. For example some vegetables (such as brussels sprouts) can stimulate first pass metabolism of some drugs, but not others. Grapefruit juice, on the other hand, may inhibit first pass metabolism of some drugs.

(4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to solubilize poorly soluble drugs and thus increase bioavailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional factors include, for example, pH-dependent solubility, site-specific intestinal permeation rate, instability to intestinal enzymes, susceptibility to first pass metabolism, and instability to colonic bacteria. Given the plethora of factors which can influence bioavailability, there usually is no way to predict, in the absence of actual testing, whether a particular drug will exhibit a food effect. For example, Toothaker and Welling, *Ann. Rev. Pharmacol. Toxicol.*, 1980, 173–99, discuss various drugs whose absorption is delayed in the presence of food (cephalexin, cefaclor, metronidazole, aspirin, alclofenac, indoprofen, digoxin, cimetidine), whose absorption may be unaffected by food (ampicillin, erythromycin estolate, spiramycin, propylthiouracil, oxazepam, bendroflumethiazide), and whose absorption is increased in the presence of food (erythromycin ethylsuccinate, nitrofurantoin, 8-methoxsalen, propranolol, metoprolol, dicoumarol, diazepam, hydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Toothaker and Welling review studies which demonstrate food related reduced absorption for tablet dosage forms of erythromycin stearate, aspirin, nafcillin, and sotalol.

In the case of azithromycin, at least one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state, and it has heretofore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at least one hour before or two hours following a meal.

It would accordingly be useful if azithromycin could be administered to patients that have eaten recently and also if a dosage form for azithromycin were available which could be administered to patients that have eaten, as well as patients in a fasted state.

SUMMARY OF THE INVENTION

This invention provides an oral dosage form of azithromycin which can be administered to a mammal (including humans) that has eaten and which exhibits substantially no adverse food effect, excluding any dosage form which contains a significant amount of an alkaline earth oxide or hydroxide. The dosage form exhibits a mean $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "$(AUC_{fed})/(AUC_{fst})$" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithromycin dosage form which does not exhibit an adverse food effect. The dosage form comprises azithromycin and a pharmaceutically acceptable carrier, as hereinafter further detailed and described. The dosage form is in the form of a tablet (including both swallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a suspension made from a unit dose packet, in the form of a powder for oral suspension, and in the form of an oral suspension per se. It is noted that when a unit dose packet is constituted, it is probably mainly in the form of a suspension if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "suspension" herein is intended to embrace liquids containing azithromycin partially in suspension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits substantially no adverse food effect. The dosage form employed exhibits a

mean (AUC_{fed})/(AUC_{fst}) of at least 0.80 with a lower 90% confidence limit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "eaten" means that the mammal has eaten food of any sort within one hour prior to dosing up to two hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra of the term "dosage form" for purposes of this invention.

Capsules as a dosage form do not form a part of the invention.

For purposes of this invention azithromycin may be administered alone or in combination with other therapeutic agents.

A food effect can be detected and quantified as described, for example in Toothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in μg/mL) of azithromycin along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient test population and are, therefore, mean values averaged over the entire test population. By measuring the area under the curve for a fed population of subjects (AUC_{fed}) and comparing it with the area for the same population of fasted subjects (AUC_{fst}), it can be determined whether a given drug exhibits an adverse food effect or not.

For definitional purposes of this invention, and specifically with respect to azithromycin dosage forms only, a dosage form of azithromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean (AUC_{fed})/(AUC_{fst}) is below the value 0.80 and/or the lower 90% confidence limit for this ratio is below 0.75.

Conversely, a dosage form of azithromycin which does not exhibit an adverse food effect is one which, when tested on a test population, exhibits a value for (AUC_{fed})/(AUC_{fst}) of at least 0.80 and a lower 90% confidence limit for this value of at least 0.75. The value for mean (AUC_{fed})/(AUC_{fst}) can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of 1.40 or below.

A population of "fed" subjects, for purposes of definition and for measuring AUC_{fed}, is one made up of subjects each of whom has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., swallowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be consumed within the twenty minute period and the subject still qualifies as "fed". A "fasted subject" for purposes of definition and for measuring AUC_{fst} is one who has not eaten for at least eight hours, typically overnight, prior to ingestion of the dosage form.

The 90% confidence limits on AUC_{fed}/AUC_{fsi} for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schuirman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was carried out using Statistical Analysis System (SAS) software from SAS Institute, Cary, N.C. SAS procedure referred to in the SAS software as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fed/Fasted) effects. The sequence effect was tested using the [subject within sequence] mean square from the analysis of variance (ANOVA) as an error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least square means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these estimates, as the difference plus (or minus) the standard error of the difference times the 95th percentile of the t-distribution with (twice the sample size-2) degrees of freedom. The anti-log was taken on the limits to obtain the corresponding confidence for the ratio.

That a dosage form according to the invention does not exhibit an adverse food effect is surprising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stomach acid. The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus, without being bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly assigned co-pending application Ser. No. 07/922,262 filed Jul. 30, 1992 discloses taste masking compositions of bitter pharmaceutical agents, such as azalide antibiotics, containing, as a taste-masking component, a basic compound selected from the group consisting of alkaline earth oxides and alkaline earth hydroxides. A composition of this invention, if it contains an alkaline earth oxide or hydroxide at all, contains less than a taste-masking amount of the taste-masking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth oxide or hydroxide, and may be free of such taste-masking component entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside these limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and also anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2.

In order to test whether a particular azithromycin dosage form exhibits an adverse food effect, the most reliable method is actually to test the dosage form in vivo on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithro-

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio $(AUC_{fed})/(AUC_{fst})$ exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds 0.75.

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution in the GI tract, or at least provides azithromycin for dissolution within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least about 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule dosage form comprising azithromycin is also considered to fall within the scope of the appended claims if it satisfies the in vitro dissolution testing requirements enumerated herein. An azithromycin dosage form according to the invention exhibits at least about 90% dissolution of azithromycin within about 30 minutes, preferably within 15 minutes, when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37° C. with paddles turning at 100 rpm. This test is described in US Pharmacopaea XXII, pp. 1578–1579. Dosage forms which pass this test under more stringent conditions (lower volume of buffer, greater amount of dosage form, lower temperature, higher pH, lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azithromycin dosage form in this in vitro test is believed to be an indicator of the time required for dissolution of the dosage form in the GI environment. The following discussion is believed pertinent in this regard.

It is generally assumed and observed that the in vitro dissolution rate of dosage forms exhibits a rank order correlation with in vivo dissolution, particularly for a single dosage form type, e.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves an important role in control of the quality of manufactured dosage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the artificial conditions of an in vitro dissolution test (e.g. vessel geometry, stirring rate, stirring method, and so forth) are not identical to the conditions under which a dosage form disintegrates and dissolves in the GI tract.

When comparing dosage forms of different type, e.g. capsules and tablets, in vitro dissolution rate should correlate roughly with in vivo dissolution rate. However, subtle differences exist between the disintegration mechanisms of capsules and tablets. For capsules, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dissolve first at the capsule ends, and later at the capsule center. Tablets, on the other hand, disintegrate homogeneously. Thus subtle differences may exist in the in vitro/in vivo dissolution correlation when comparing capsules and tablets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may exhibit subtle differences in in vivo dissolution rate. While such subtle differences may have no therapeutically significant effect on systemic bioavailability of an orally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-containing capsules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally dosed. In fact, this has been observed for azithromycin, as exemplified in the Examples herein.

For the in vitro dissolution studies disclosed herein, azithromycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chromatographic column (15 cm×0.4 cm), and a 5 micron alumina based hydrocarbonaceous spherical particle precolumn (5 cm×0.4 cm) (both available from ES Industries, Marlton, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonitrile (pH 11) was used, with electrochemical detection (e.g. Bioanalytical Systems, West Lafayette, Ind., LC-4B amperometric detector with dual series glassy carbon electrodes).

For in vivo food effect studies, serum azithromycin is assayed using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog. Biomed. Appl. 565, 321–337, with amperometric electochemical detection. Alternatively, any assay method that produces equivalent results, for example, bioassay, can be used.

Tablets according to the invention contain, as necessary ingredients, azithromycin and a disintegrant. Examples of tablet disintegrants are starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (sodium croscarmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), clays (e.g. magnesium aluminum silicate), microcrystalline cellulose (of the type available under the registered trademark Avicel from FMC Corp. or the registered trademark Emcocel from Mendell Corp., Carmel, N.Y.), alginates, gums, surfactants, effervescent mixtures, hydrous aluminum silicate, cross-linked polyvinylpyrrolidone (available commercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Preferred disintegrants for azithromycin tablets are sodium croscarmellose (Ac-Di-Sol), sodium starch glycolate (available commercially under the registered trademarks Primojel from Avebe (Union, N.J.) or Generichem, (Little Falls, N.J.) and Explotab from Mendell Corp.), microcrystalline cellulose (Avicel), and cross-linked polyvinylpyrrolidone (PVP-XL). Azithromycin tablets of this invention comprise azithromycin and 1–25% disintegrant, preferably 3–15% disintegrant based on total tablet weight. For example, a 463.5 mg tablet (250 mg activity azithromycin) may contain 9 mg sodium croscarmellose and 27 mg pregelatinized starch.

In addition to the active ingredient azithromycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the exact formulation, such as binders, flavorings, buffers, diluents, colors, lubricants, sweetening agents, thickening agents, and glidants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Examples of binders are acacia, cellulose derivatives (such as methylcellulose and carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose), gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, starch paste, sucrose, sorbitol, pregelatinized starch, gum tragacanth,

alginic acids and salts thereof such as sodium alginate, magnesium aluminum silicate, polyethylene glycol, guar gum, bentonites, and the like. A preferred binder for azithromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Point, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth. The amount of flavoring may depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by weight based on the total tablet weight, when a flavor is used.

A variety of materials may be used as fillers or diluents. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. starch 1500), cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emcompress from Mendell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Monmouth Junction, N.J.), calcium carbonate, calcium sulfate, and others as known in the art.

Lubricants can also be employed herein in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants are magnesium stearate, stearic acid, glycerylbehaptate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art. Preferred lubricants are magnesium stearate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise 0.5 to 7.0% of the total tablet weight.

Other excipients such as glidants and coloring agents may also be added to azithromycin tablets. Coloring agents may include titanium dioxide and/or dyes suitable for food such as those known as F. D. & C, dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be added extragranularly. Alternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tablets may also be coated, with a coating that exhibits little or no effect on or interference with tablet dissolution, to assure ease of swallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are film-coated to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropylmethylcellulose (HPMC). HPMC may be obtained commercially, for example from Colorcon Corp., in coating formulations containing excipients which serve as coating aids, under the registered trademark Opadry. Opadry formulations may contain lactose, polydextrose, triacetin, polyethyleneglycol, polysorbate 80, titanium dioxide, and one or more dyes or lakes. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press. Tablet formulation and conventional processing techniques have been widely described, for Example in *Pharmaceutical Dosage Forms: Tablets;* Edited By Lieberman, Lachman, and Schwartz; Published by Marcel Dekker, Inc., 2d Edition, Copyright 1989, the text of which is herein incorporated by reference.

The azithromycin dosage forms of this invention also include powders to make oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-caking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmacist. The oral suspension is thus the actual dosage form ingested by patients. The typical shelf life for a suspension is about five days because azithromycin therapy is generally of five days duration.

Azithromycin suspensions according to the invention contain, as necessary ingredients in addition to azithromycin, one or more thickening agents in a total amount of 0.1 to 2%, and a buffer or pH-altering agent in an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used in an amount from 0.1 to 2%.

Suitable thickening agents function as suspending agents and include, for example, hydrocolloid gums known for such purpose, examples of which include xanthan gum, guar gum, locust bean gum, gum tragacanth, and the like. Alternatively, synthetic suspending agents may be used such as sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like.

Dispersing agents include colloidal silicon dioxide, available from Cabot Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masked by including a basic buffer or pH-altering agent which will provide a pH of approximately 10 in the constituted suspension. Maintenance of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masks the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mask the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, artificial creme de vanilla #11489, and spray-dried artificial banana #15223 available commercially from Bush Boake Allen, Inc., Chicago, Ill. Artificial sweeteners may also be used.

A powder used to make a suspension herein may also contain conventional optional ingredients such as (1) wetting agents such as sorbitan monolaurate, polysorbate 80, and sodium lauryl sulfate; (2) anti-foaming agents and (3) sweeteners and fillers such as glucose. The powder may also contain a buffer to maintain a high pH upon reconstitution, as discussed above. Suitable buffers and pH-altering agents

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