Title: TASTE MASKED GRANULES COMPRISING CLARITHROMYCIN, HYDROCOLLOIDS AND A COATING

Abstract: The present invention relates to taste masked granules comprising a) a core comprising clarithromycin, one or more hydrocolloids, one or more pharmaceutically acceptable excipients (ratio clarithromycin: hydrocolloid- 1: 0.2- 1: 10) b) a coating over the core containing one or more pH dependent polymers that release clarithromycin at a pH above 4.5.
TASTE MASKED GRANULES COMPRISING CLARITHROMYCIN, HYDROCOLLOIDS AND A COATING

Field of Invention

The present invention relates to taste masked granules comprising poorly soluble, bitter tasting pharmaceutical ingredients, and oral suspension compositions thereof. Also provided are processes for the preparation of taste masked granules and use of the granules to treat a bacterial infection.

Background of the Invention

Erythromycin and its derivatives, in particular, 6-O-methoxyerythromycin A (clarithromycin), are known for their antibacterial activity against a number of organisms. These compounds have a bitter taste which can result in poor compliance of the regimen or selection of another, possibly less effective, therapeutic agent.

Liquid suspension dosage forms have stability problems associated with maintaining the drugs in suspension. Poorly formulated liquid pharmaceutical suspensions allow the drug to sediment and may not properly redisperse, thereby affecting the therapeutic concentration of the drug in suspension. This may result in underdosing or overdosing of the patient, which may seriously compromise the patient’s recovery.

United States Patent No. 4,808,411 describes a taste-masked composition comprising 95% of erythromycin or a derivative thereof and about 5% to about 75% of a carbomer. The drug and carbomer form a complex which is further taste-masked by a coating.

United States Patent No. 4,925,675 relates to pharmaceutically active microencapsulated granules comprising erythromycin and a high density binder in a ratio of from about 5:1 to about 15:1.

United States Patent application 2003/0099715 discloses taste-masked pellets of granulated particles comprising a pharmaceutically active compound and an organic carboxylic, surfactant and a hydrocolloid. The pellets are disclosed as being coated with an enteric film.
There still exists a need for a taste masked suspension dosage form that minimizes sedimentation of the pharmaceutically active agent, provides uniform distribution of the active agent and has a palatable taste. In addition to the full concealment of the bitter taste, a rapid and complete release is critical for the beneficial effects of an active ingredient to be made bioavailable to a patient.

Summary of the Invention

In one general aspect there is provided granules that include a core comprising clarithromycin, one or more hydrocolloids and one or more pharmaceutically acceptable excipients. The clarithromycin and one or more hydrocolloids are present in a ratio from about 1:0.2 to about 1:10, and a coating over the core comprises one or more pH dependent polymers that release clarithromycin at a pH above 4.5.

Embodiments of the present invention may have one or more of the following features. For example, the core may further include one or more inert carrier particles.

The inert carrier particles may include one or more of nonpareil seeds, sucrose spheres, lactose, xylitol, mannitol, dicalcium phosphate, silica gel, microcrystalline seeds and ion exchange resins.

The clarithromycin may have a particle size less than about 100 μm or it may have a particle size less than about 30 μm. The clarithromycin may be present at a concentration from about 5% to about 90% w/w of the core.

The one or more hydrocolloids may include polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and mixtures thereof. The polysaccharides may include one or more of alginic acid, sodium alginate, and calcium alginate. The cellulose and cellulose derivatives may include ethylcellulose, methyl cellulose, hydroxypropymethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and carboxymethylcellulose (CMC).

The one or more pharmaceutically acceptable excipients may include binders, diluents/fillers, glidants, disintegrants and lubricants.
The pH dependent coating may include from about 5% to about 50% w/w of the granule. The one or more pH dependent polymers may include one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, (meth) acrylic acid and acrylic acid copolymers, cellulose acetate trimellitate, shellac and mixtures thereof.

The coating may further include one or more of plasticizers, glidants or flow regulators and lubricants. The granules may be incorporated into a dry powder, syrup, suspension, or tablets.

In another general aspect there is provided a process for the preparation of granules. The process includes granulating clarithromycin, one or more hydrocolloids, and one or more pharmaceutically acceptable excipients to form a core, and applying one or more pH dependent polymers to form a coating on to the core.

Embodyments of the present invention may have one or more of the following features. For example, the clarithromycin and one or more hydrocolloids may be present in a ratio from about 1:0.2 to about 1:10. The core may be formed by wet granulation, extrusion, and spherization.

The one or more hydrocolloids may include polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and mixtures thereof. The polysaccharides may include one or more of alginic acid, sodium alginate, and calcium alginate. The cellulose and cellulose derivatives may include ethylcellulose, methyl cellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and carboxymethylcellulose (CMC).

The one or more pH dependent polymers may include one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, (meth) acrylic acid and acrylic acid copolymers, cellulose acetate trimellitate, shellac, and mixtures thereof.

The coating may further include one or more of plasticizers, glidants or flow regulators and lubricants.
In another general aspect there is provided a process for the preparation of granules. The process includes preparing a solution of clarithromycin, one or more hydrocolloids, and one or more pharmaceutically acceptable excipients, layering inert carrier particles with the solution to form a core and applying one or more pH dependent polymers to form a coating.

Embodiments of the present invention may include one or more of the following features. For example, the one or more hydrocolloids may include polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and mixtures thereof.

The one or more pH dependent polymers may include one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, (meth) acrylic acid and acrylic acid copolymers, cellulose acetate trimellitate, shellac, and mixtures thereof.

The coating may further include one or more of plasticizers, glidants or flow regulators, and lubricants.

In another general aspect there is provided a pharmaceutical composition. The pharmaceutical composition includes granules which include a core comprising clarithromycin and one or more hydrocolloids, a coating over the core and a suspension medium. The clarithromycin and the one or more hydrocolloid are present in a ratio from about 1:0.2 to about 1:10 and the coating over the core comprising one or more pH dependent polymers that release clarithromycin at a pH above 4.5.

Embodiments of the present invention may include one or more of the following features. For example, the suspending medium may include one or more of suspending agents, structuring agents, wetting agents, solubilizers, sweetening agents, buffers, flavors, coloring agents, disintegrant and preservatives.

In yet another general aspect there is provided a method of treating bacterial infections in a mammal in need thereof. The method includes administering a pharmaceutical composition comprising granules, wherein the granules include a core comprising clarithromycin and one or more hydrocolloids, and a coating over the core. The clarithromycin and the one or more hydrocolloids are present in a ratio from about 1:0.2 to
about 1:10. The coating comprises one or more pH dependent polymers that release clarithromycin at a pH above 4.5.

Embodiments of the present invention may include one or more of the following features. For example, the pharmaceutical composition may further include one or more of omeprazole, ansamycin, amoxycillin, tetracycline, chloramphenicol, ciprofloxacin, ethambutol, ritonavir, rifampicin and metronidazole.

**Detailed Description of the Invention**

In the present invention granules are provided that may be formulated into a liquid suspension, thereby allowing prompt release of the active agent. The present invention provides granules of a clarithromycin, which include a core comprising clarithromycin and one or more hydrocolloids, a coating over the core, which includes one or more pH dependent polymers. The granules may be used with a suspending medium to form a pharmaceutical composition. The composition provided is sufficiently able to preserve the taste masking effect for a period of at least 14 days after reconstitution.

Taste masked granules refer to the particles that include clarithromycin having a reduced bitter taste. The granules may range in size from about 200 µm to about 1000 µm. For example, the granules may range in size from about 250 µm to about 500 µm.

Clarithromycin may be prepared by any known method, for example, using any of the procedures disclosed in United States Patent No. 4,331,803 or United States Patent No. 4,672,109, which are hereby incorporated in their entirety by reference.

The particle size of clarithromycin may be less than about 100 µm, for example, less than about 50 µm or less than about 30 µm. The clarithromycin used in the granules described herein may be present at a concentration of from about 5% to about 90% w/w of the core, for example from about 10% to about 75% w/w of the core.

Suitable hydrocolloids may include one or more natural and synthetic polymers, which form colloidal solutions in aqueous systems. Suitable hydrocolloids include polyvinyl pyrrolidones; starch; polysaccharides, such as alginic acid, sodium alginate, and calcium alginate; cellulose and cellulose derivatives, such as ethylcellulose, methyl cellulose,
hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and
carboxymethylcellulose (CMC); or mixtures thereof. The one or more hydrocolloids may be
present at a concentration of from about -10% to about 30% w/w of the core. In addition, the
clarithromycin and the one or more hydrocolloids may be present in a ratio from about 1: 0.2
to about 1: 10 and particularly from about 1:0.5 to about 1: 5.

The core may be prepared by granulating clarithromycin and the one or more
hydrocolloids together using any conventional technique, including wet granulation,
extusion, and spheronization. Alternatively, it may include one or more inert carrier particles
on which suspension, solution or dispersion of clarithromycin and hydrocolloids may be
layered.

Suitable inert carrier particles include one or more of nonpareil seeds, lactose, xylitol,
mannitol, dicalcium phosphate, sucrose spheres, silica gel, microcrystalline seeds and ion
exchange resins.

The core composition may further include one or more pharmaceutically acceptable
excipients in addition to clarithromycin and hydrocolloids. Suitable pharmaceutical
acceptable excipients - include one or more of binders, diluents/fillers, glidants, disintegrants
and lubricants.

Suitable binders for granulation and core formation include one or more of
polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), low viscosity
hydroxypropyl cellulose (HPC), gelatin, and cornstarch.

Aqueous or pharmaceutically acceptable solvent mediums may be used for preparing
the core particles. Water may be mixed with organic solvents and used as a solvent for
granulation.

The core may be coated with a pH dependent coating that provides a protective layer
which remains stable in the acid environment of the stomach. The coating is readily soluble
in the intestine (pH above 4.5) and thereby provides for immediate release of the active agent
in the intestine. The coating may be present at a concentration from about 5% to about 50%
w/w. For example, the coating may be present from about 20% to about 45% w/w of granules.

The pH dependent coating may include one or more pH dependent polymers. Suitable pH dependent polymers include cellulose and its ester derivatives (e.g. cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate), polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methamethacrylate copolymers and shellac. The polymers may be used as a dry powder or an aqueous dispersion or solution. Some commercially available materials that may be used include methacrylic acid copolymers available under the trade name Eudragits (L100, S100, L30D) manufactured by Rohm Pharma, Cellacefate (cellulose acetate phthalate) from Eastman Chemical Co., Aquateric (cellulose acetate phthalate aqueous dispersion) from FMC Corp., and Aqoat (hydroxypropyl methylcellulose acetate succinate aqueous dispersion) from Shin Etsu K.K.

The pH dependent coating may additionally include one or more water insoluble polymers in addition to one or more pH dependent polymers.

Suitable water insoluble polymers include cellulose acetate, ethylcellulose, and Eudragit RS (poly ethyl acrylate: methyl methacrylate: trimethylammoniethyl methacrylatechloride 1:2:0.1).

The coating composition may further include one or more of plasticizers, glidants or flow regulators, and lubricants.

Suitable plasticizers include one or more of triacetin, tributyl citrate, triethyl citrate, acetyl tri-butyl citrate diethyl phthalate, castor oil, dibutyl sebacate, acetylated monoglycerides, polyethylene glycol, and mixtures thereof.

Suitable flow regulators or glidants include one or more of silicon dioxide, magnesium trisilicate, powdered cellulose, rice starch, talc, tri basic calcium phosphate, and mixtures thereof.

Suitable lubricants include one or more of calcium stearate, glyceryl monostearate, mineral oils, polyethylene glycols, talc, stearic acid, zinc stearate, magnesium stearate, and mixture thereof.
The coating is applied to the core as a solution, a suspension or dispersion in a suitable solvent. The solvents for the coating solution may include water, an organic solvent and mixtures thereof. Suitable organic solvents include lower alcohols, such as methyl alcohol, ethyl alcohol, isopropyl alcohol and n-butyl alcohol; lower alkanones, such as acetone; acetonitrile; chloroform; and methylene chloride. For example, ethyl alcohol and isopropyl alcohol may be used.

The coatings may be applied to the core using any of the coating techniques conventionally used in the pharmaceutical industry including fluidized bed coating, pan coating, spray coating or hot melt.

The oral taste masked coated granules may be optionally seal coated with one or more a film forming polymers including hydroxypropyl methylcellulose, shellac, and hydroxypropyl cellulose.

The oral taste masked granules are capable of being administered as coated granules dry syrups, sachets, tablets and powders that can be reconstituted before usage as a liquid suspension. The reconstitutable compositions prepared from granules are stable during storage and the suspensions, once reconstituted, present a masked taste during the entire course of treatment.

The compositions are prepared by blending the taste-masked granules with a suitable suspending medium which may include one or more of suspending/structuring agents, wetting agents / solubilizers, sweetening agents, buffers, flavors, coloring agents, disintegrants, anti adherents, and preservatives.

Suitable suspending and structuring agents include one or more of gum, cellulose ether, alginates, carboxomers, starch, proteins, dextrins, gelatin, chitosan, agar and mixture thereof.

Suitable cellulose ethers include hydroxy ethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose. Suitable gums include guar gum, locust bean gum, gum tragacanth, xanthan gum, and the mixtures thereof. Suitable dextrins include
maltodextrin and its salts, such as maltodextrin alginates. For example, xanthan gum and maltodextrin may be used as suspending and structuring agents.

Wetting agents or solublizers, which help to wet the particles and let fluid penetrate into the agglomerate of particles, may include cyclodextrins, lecithins, sucrose, mannitol, and sorbitol.

Suitable disintegrants include one or more of cross linked carboxymethyl sodium, crosslinked polyvinyl pyrrolidone, carboxymethyl starch, low substituted hydroxypropyl cellulose, sodium starch glycolate, and mixtures thereof.

Anti adherents, such as colloidal silicon dioxide, is may be present at a concentration of from about 0.2% to 2.0%. For example, the anti-adherent may be present at a concentration from about 0.2% to about 0.8%, or from about 0.4% to about 0.7%, by weight based on the total weight of the suspension.

Suitable sweetening agents include sugars, such as monosaccharides, disaccharides and polysaccharides. For examples suitable sugars may include xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch or corn syrup solids, and sugar alcohols, such as sorbitol, xylitol, mannitol, glycerin, and mixtures thereof. Water soluble artificial sweeteners also may be employed in place of, or in addition to, sugar sweeteners. Suitable artificial sweeteners include aspartame, sucralose, cyclamates, saccharin, and mixtures thereof.

Suitable flavoring agents include menthol, peppermint, mint flavors, both natural and/or artificial fruit flavors e.g., cherry, grape, orange, strawberry, tutti frutti, chocolate, vanilla, bubblegum flavor, and coffee flavor.

Coloring agents also may be incorporated in the suspension to provide an appealing color to the suspension. Suitable colors and flavors selected should be FDA approved and compatible with the active compound and other excipients.

Suitable preservatives include sodium benzoate, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium edetate) and parabens (such as
methyl, ethyl, propyl and butyl p-hydroxybenzoic acids esters), potassium sorbate, potassium sorbate, and mixtures thereof.

Suitable buffers include citric acid, sodium citrate, ascorbic acid, potassium phosphate or sodium phosphate, and electrolytes, such as sodium chloride, potassium chloride, and sodium bicarbonate.

The final suspension would may include from about 100 mg to about 500 mg of clarithromycin per 5 mL of suspension. For example, the suspension may include from about 125 mg to about 250 mg of clarithromycin per 5 mL of suspension.

In addition, the composition may further include one or more additional antibiotics or antimicrobial agent including omeprazole, ansamycin, amoxycillin, tetracycline, chloramphenicol, ciprofloxacin, ethambutol, ritonavir, rifampicin and metronidazole.
### Example 1

**Taste masked granules of clarithromycin:**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Inert carrier particle</td>
<td></td>
</tr>
<tr>
<td>2 Sucrose sphere (60-80#)</td>
<td>27.37</td>
</tr>
<tr>
<td>2 Drug Layer (Layer I)</td>
<td></td>
</tr>
<tr>
<td>3 Clarithromycin</td>
<td>26.32</td>
</tr>
<tr>
<td>4 Hydroxypropyl methyl cellulose</td>
<td>5.68</td>
</tr>
<tr>
<td>5 Hydroxypropyl cellulose</td>
<td>1.05</td>
</tr>
<tr>
<td>6 Polyvinyl pyrrolidone (K-30)</td>
<td>1.05</td>
</tr>
<tr>
<td>6 Alginic Acid</td>
<td>7.90</td>
</tr>
<tr>
<td>7 Purified Water</td>
<td>q.s</td>
</tr>
<tr>
<td>8 Acetone</td>
<td>q.s</td>
</tr>
<tr>
<td>9 Coating layer (layer II)</td>
<td></td>
</tr>
<tr>
<td>9 Hydroxypropyl methylcellulose phthalate</td>
<td>28.42</td>
</tr>
<tr>
<td>10 Castor Oil</td>
<td>1.42</td>
</tr>
<tr>
<td>11 Colloidal Silicon Dioxide</td>
<td>0.79</td>
</tr>
<tr>
<td>12 Acetone</td>
<td>q.s</td>
</tr>
<tr>
<td>13 Purified Water</td>
<td>q.s</td>
</tr>
</tbody>
</table>
Procedure:

I Preparation of taste masked granules:

(a) Hydroxypropyl methylcellulose, hydroxypropyl cellulose, and polyvinyl pyrrolidone were dissolved in water,

(b) Acetone was added to the mixture of step (a),

(c) Alginic acid was dispersed gradually under constant stirring to step (b), until a uniform suspension was obtained,

(d) Clarithromycin was dispersed in the suspension obtained from step (c) under constant stirring,

(e) The clarithromycin dispersion obtained from step (d) was sprayed onto sucrose sphere to form granules in a fluid bed processor to achieve a build up of approximately 44.16%,

(f) Granules obtained from step (e) were dried in Vacuum tray dryer till level of detection was NMT 3% at 105°C.

Coating layer:

(g) Hydroxypropyl methylcellulose phthalate and castor oil were dissolved in acetone,

(h) Under constant stirring colloidal silicon dioxide was dispersed in the solution of step (g),

(i) The dried granules obtained from step (f) were sprayed with the coating solution of step (h) using a Gansons Fluid bed processor to achieve a build up of approximately 44.16%,

(j) The coated granules of clarithromycin were dried at 50°C in a vacuum tray dryer till LOD is NMT 3% at 105°C.
II) Preparation of blend for suspension (125 mg/5 mL)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clarithromycin coated granules</td>
<td>13.57</td>
</tr>
<tr>
<td>2 Sucrose</td>
<td>71.18</td>
</tr>
<tr>
<td>3 Aspartame</td>
<td>0.57</td>
</tr>
<tr>
<td>4 Xanthan Gum</td>
<td>0.03</td>
</tr>
<tr>
<td>5 Colloidal Silicon Dioxide</td>
<td>0.57</td>
</tr>
<tr>
<td>6 Sodium Citrate</td>
<td>0.27</td>
</tr>
<tr>
<td>7 Citric Acid USP</td>
<td>0.09</td>
</tr>
<tr>
<td>8 Sodium Benzoate</td>
<td>0.29</td>
</tr>
<tr>
<td>9 Titanium Dioxide</td>
<td>0.86</td>
</tr>
<tr>
<td>10 Flavour</td>
<td>0.51</td>
</tr>
<tr>
<td>11 Sodium Chloride</td>
<td>0.34</td>
</tr>
<tr>
<td>12 Cross linked carboxymethyl cellulose sodium</td>
<td>3.43</td>
</tr>
<tr>
<td>13 Maltodextrin</td>
<td>8.29</td>
</tr>
</tbody>
</table>

Procedure:

1. Sucrose was dried at 50°C - 60°C and sifted through BSS#18,
2. A part of the sucrose was mixed with sodium benzoate, sodium citrate, citric acid and sodium chloride and passed through a cadmill,
3. To the mixture of step 2, aspartame, xanthan gum, maltodextrin, cross linked carboxymethyl cellulose sodium, colloidal silicon dioxide, titanium dioxide, flavour were added, mixed and sifted through BSS#44,
4. Clarithromycin granules were sifted through BSS#18 and blended with the mixture of step 3 and the remaining mixture of step (2),
5. The clarithromycin suspension obtained from step 4 was filled in bottles.
Example 2

I) Taste masked granules of clarithromycin: As per example 1

II) Preparation of blend for suspension (250 mg/5 mL)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clarithromycin coated granules</td>
<td>27.14</td>
</tr>
<tr>
<td>2 Sucrose</td>
<td>57.61</td>
</tr>
<tr>
<td>3 Aspartame</td>
<td>0.57</td>
</tr>
<tr>
<td>4 Xanthan Gum</td>
<td>0.03</td>
</tr>
<tr>
<td>5 Colloidal Silicon Dioxide</td>
<td>0.57</td>
</tr>
<tr>
<td>6 Sodium Citrate</td>
<td>0.27</td>
</tr>
<tr>
<td>7 Citric Acid</td>
<td>0.09</td>
</tr>
<tr>
<td>8 Sodium Benzoate</td>
<td>0.29</td>
</tr>
<tr>
<td>9 Titanium Dioxide</td>
<td>0.86</td>
</tr>
<tr>
<td>10 Flavor</td>
<td>0.51</td>
</tr>
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<td>3.43</td>
</tr>
<tr>
<td>13 Maltodextrin</td>
<td>8.29</td>
</tr>
</tbody>
</table>

Procedure: As described for Example 1.

5 In vivo biological studies

In a randomized, single dose, two-way crossover study, the relative bioavailability (rate and extent of absorption) of the clarithromycin suspension 125 mg/5 mL (T), as prepared according to Example 1 was compared with the reference Biaxin® granules for oral suspension (R), (125 mg/5 mL) (Abbott) in 15 healthy male subjects under non-fasting (fed) and fasting conditions.
Table 1: Bioavailability study under fasting conditions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC₀-₄ (%)</th>
<th>AUC₀-∞ (%)</th>
<th>Cₘₐₓ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/R ratio</td>
<td>94.53</td>
<td>94.21</td>
<td>96.28</td>
</tr>
<tr>
<td>90% confidence (%)</td>
<td>(84.02-106.36)</td>
<td>(83.73-106.01)</td>
<td>(83.84-110.56)</td>
</tr>
</tbody>
</table>

Table 2: Bioavailability study under fed conditions

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC₀-₄ (%)</th>
<th>AUC₀-∞ (%)</th>
<th>Cₘₐₓ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/R ratio</td>
<td>99.64</td>
<td>99.60</td>
<td>107.50</td>
</tr>
<tr>
<td>90% confidence (%)</td>
<td>91.19-108.87</td>
<td>91.01-108.99</td>
<td>94.28-122.57</td>
</tr>
</tbody>
</table>

Formulation (T): as described in Example 1

Reference (R): Abbott’s Biaxin granules for oral suspension (125/5 mL)

The results of pharmacokinetic studies indicate bioequivalence (within the 80-125% FDA-acceptance criterion) between Test (Example 1 formulation) and Reference (Abbott’s Biaxin® suspension).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.
We Claim:

1. Granules comprising:
   (a) a core comprising clarithromycin, one or more hydrocolloids and one or more pharmaceutically acceptable excipients, wherein the clarithromycin and one or more hydrocolloids are present in a ratio from about 1:0.2 to about 1:10; and
   b) a coating over the core comprising one or more pH dependent polymers that release clarithromycin at a pH above 4.5.

2. The granules according to claim 1, wherein the core further comprises one or more inert carrier particles.

3. The granules according to claim 1, where the one or more inert carrier particles comprise one or more of nonpareil seeds, sucrose spheres, lactose, xylitol, mannitol, dicalcium phosphate, silica gel, microcrystalline seeds and ion exchange resins.

4. The granules according to claim 1, wherein the clarithromycin has a particle size less than about 100 μm.

5. The granules according to claim 4, wherein the clarithromycin has a particle size less than about 30 μm.

6. The granules according to claim 1, wherein the clarithromycin comprises from about 5% to about 90% w/w of the core.

7. The granules according to claim 1, wherein the one or more hydrocolloids comprise polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and mixtures thereof.

8. The granules according to claim 7, wherein the polysaccharides comprise one or more of alginic acid, sodium alginate, and calcium alginate.

9. The granules according to claim 7, wherein the cellulose and cellulose derivatives comprise one or more of ethylcellulose, methyl cellulose, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), and carboxymethylcellulose (CMC).
10. The granules according to claim 1, wherein the one or more pharmaceutically acceptable excipients comprise binders, diluents/ fillers, glidants, disintegrants, and lubricants.

11. The granules according to claim 1, wherein the pH dependent coating comprises from about 5% to about 50% w/w of the granule.

12. The granules according to claim 1, wherein the one or more pH dependent polymers comprise one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, (meth) acrylic acid and acrylic acid copolymers, cellulose acetate trimellitate, shellac and mixtures thereof.

13. The granules according to claim 1, wherein the coating further comprises one or more of plasticizers, glidants or flow regulators, and lubricants.

14. The granules according to claim 1, wherein the granules are incorporated into one or more of a dry powder, syrup, suspension or tablet.

A process for the preparation of granules, the process comprising:

(a) granulating clarithromycin, one or more hydrocolloids, and one or more pharmaceutically acceptable excipients to form a core; and

(b) applying one or more pH dependent polymers to the core to form a coating on the core.

16. The process according to claim 15, wherein the clarithromycin and one or more hydrocolloids are present in a ratio from about 1:0.2 to about 1:10.

17. The process according to claim 15, wherein the core may be formed by wet granulation, extrusion, and spherolization.

18. The process according to claim 15, wherein the one or more hydrocolloids comprise polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and mixtures thereof.

19. The process according to claim 15, wherein the coating further comprises one or more of plasticizers, glidants or flow regulators and lubricants.
20. A process for the preparation of granules, the process comprising:
   (a) preparing a solution of clarithromycin, one or more hydrocolloids, and one or more
       pharmaceutically acceptable excipients;
   (b) layering inert carrier particles with the solution obtained; and
   (c) coating the core with one or more pH dependent polymers.

21. The process according to claim 20, wherein the one or more hydrocolloids comprise
    polyvinyl pyrrolidones, starch, polysaccharides, cellulose and cellulose derivatives, and
    mixtures thereof.

22. The process according to claim 20, wherein the one or more pH dependent polymers
    comprise one or more of cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate,
    hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, (meth) acrylic
    acid and acrylic acid copolymers, cellulose acetate trimellitate, shellac, and mixtures thereof.

23. The process according to claim 20, wherein the coating further comprises one or more
    of plasticizers, glidants or flow regulators and lubricants.

24. A pharmaceutical composition comprising granules and a suspension medium, the
    granules comprising:
    (a) a core comprising clarithromycin and one or more hydrocolloids, wherein
        the clarithromycin and the one or more hydrocolloid are present in a ratio from
        about 1:0.2 to about 1:10;
    b) a coating over the core comprising one or more pH dependent polymers that
        release clarithromycin at a pH above 4.5.

25. The pharmaceutical composition according to claim 24, wherein the suspending
    medium comprises one or more of suspending agents, structuring agents, wetting agents,
    solubilizers, sweetening agents, buffers, flavors, coloring agents, disintegrant and
    preservatives.

26. A method of treating bacterial infections in a mammal in need thereof, the method
    comprising administering a pharmaceutical composition comprising granules, wherein the
    granules comprise:
(a) a core comprising clarithromycin and one or more hydrocolloids, wherein clarithromycin and the one or more hydrocolloid are present in a ratio from about 1:0.2 to about 1:10; and
(b) a coating over the core comprising one or more pH dependent polymers that release clarithromycin at a pH above 4.5.

27. The method of treating bacterial infections according to claim 29, wherein the pharmaceutical composition further comprises one or more of omeprazole, ansamycin, amoxycillin, tetracycline, chloramphenicol, ciprofloxacin, ethambutol, ritonavir, rifampicin and metronidazole.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

A61K9/16  A61P31/04

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Date of the actual completion of the International search**

15 December 2005

**Date of mailing of the International search report**

04/01/2006

**Name and mailing address of the ISA**

European Patent Office, P.B. 5816 Patentlaan 2
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**Authorized officer**

Schifferer, H
**Box II** Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 26,27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III** Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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