Title: ORAL TASTE MASKED PHARMACEUTICAL COMPOSITIONS

Abstract: The present invention relates to oral taste masked pharmaceutical compositions that include a core having an active ingredient coated with a mixture of polymeric film forming binders and inorganic carriers. Also provided are processes for preparing the oral taste masked pharmaceutical composition.
ORAL TASTE MASKED PHARMACEUTICAL COMPOSITIONS

Field of the Invention

The present invention relates to oral taste masked pharmaceutical compositions that include a core having an active ingredient coated with a mixture of polymeric film forming binders and inorganic carriers. Also provided are processes for preparing the oral taste masked pharmaceutical composition.

Background of the Invention

Pharmaceutical compositions intended for oral use are usually administered either in the form of liquid dosage forms, such as a syrup, suspension, or emulsion, or solid dosage forms, such as a capsule, compressed tablet, granule, etc. A variety of systems for film coating and incorporation of a powder blend into a hard gelatin shell have been widely adapted in the past in order to block the active ingredient from the taste buds. These methods attempted to restrict the bitter taste sensed by the patient.

When the pharmaceutical composition is to be used by geriatric and/or pediatric patient populations, the problem of dysphasia is prevalent, and it becomes imperative for the formulator to take into account the disagreeable taste of the active ingredient. For patient-friendly delivery of bitter tasting active ingredients in liquid or rapid disintegrating dosage forms, work must be done at the particle level in order to mask the unpleasant taste. The prior art is replete with attempts to achieve an effective and commercially viable method of taste masking. While formulating an oral taste masked composition with a taste masking coating, attention must be paid to regulation of the release profile, as the active ingredient may be released too quickly, or conversely, in a delayed manner. Therefore, taste masking is linked to the dosage forms release profile. This profile in an oral taste masked composition depends largely on the percent of weight build up of the coating composition on the core, as well as the type of coating polymers used.

Many methods have been used in the prior art to achieve the taste masking effect, such as the use of ion exchange resins, salt and ester conjugation, lipids, solid dispersions, and microencapsulation by coacervation. The development of an oral solid, rapidly disintegrating formulation requires a coating to be applied on the particles. This coating must have sufficient elastic strength to withstand the compression pressure during tableting in order to avoid rupturing the film.
The development of a liquid oral system presents the formulator with several issues. First, the leaching of the active ingredient from the microcapsules may spoil the organoleptic properties. Second, the swelling of the polymeric film may lead to poor physical stability and caking of particles on sedimentation. Finally, by overcoming the first two issues with insoluble film formers, a new difficulty arises while developing a rapid release dosage form. The limited availability of liquid taste masked formulations on the market shows a real need for the development of a taste masking system that is applicable to a wide range of pharmaceutical dosage forms.

U.S. Patent No. 6,197,348 describes a dosage form that utilizes encapsulated particles coated with polymers, such as Eudragit RS and Eudragit RL. Taste masking is achieved as a result of the polymer coatings and a liquid suspending medium having a pH that is adjusted to a point where the active ingredient is insoluble. However, the thickness and type of coating is not sufficient for taste masking.

EP 0458751 discloses compositions containing a core that includes a cyclic amino acid compound. The core is coated with polymeric film forming compounds and hydrophilic fats, fatty acids and waxes.

U.S. Patent No. 4,800,087 discloses a taste masked composition in a chewable dosage form having a controlled release profile. The invention utilizes a combination of polymers to achieve a taste masking coating suitable for incorporation into a chewable dosage form. The composition contains microcapsules which are composed of an active ingredient and a polymer mixture coating having a sufficient elasticity to withstand chewing. The polymeric coating mixture includes one high temperature film forming copolymer and one low temperature film forming copolymer.

U.S. Patent No. 6,139,865 discloses a taste masked microcapsule composition of water soluble active ingredients. The water soluble active ingredients are coacervated in the polymeric material. This technique suffers from several disadvantages. For example, the technique requires the use of hydrocarbons and other organic solvents, such as cyclohexane. These solvents are explosive and present problems in large scale manufacturing.

U.S. Application 2002/064563 discloses a taste masked composition of topiramate and a process for its preparation. The process includes preparing core particles which
include the active ingredient topiramate, coating with a taste masked mixture to form coated particles, and drying the coated particles.

U.S. Patent No. 6,106,861 discloses a multiparticulate disintegrating tablet which includes excipients and an active ingredient in the form of microcrystals. Only a limited number of active ingredients can be commercially made in the form of microcrystals, and specifically, amorphous powders cannot be utilized in this process.

WO 01/35930 discloses a process for taste masking by granulation of the active ingredient with an aqueous admixture that includes a neutral methacrylic acid ester copolymers and a binder. Taste masking can only be achieved for moderately bitter and poorly soluble active ingredients, but is ineffective for highly bitter and/or soluble active ingredients.

U.S Patent No. 5,084,278 describes a chewable taste masked pharmaceutical composition having a controlled release profile. The composition comprises microcapsules with are made up of an active ingredient core coated with a polymer mixture. The coating includes a blend of ethyl cellulose and polymethacrylic acid ester copolymers.

U.S. Patent No. 6,136,347 describes a pharmaceutical composition which comprises microcapsules wherein the active ingredient is microencapsulated within the microcapsule wall. The active ingredient is present as an anhydrate or its free base form. The composition further utilizes an oily suspension as a vehicle for suspending microparticles coated with a combination of water soluble and water insoluble polymers, thus preventing the interaction of water. However, this dosage form suffers from the disadvantage of poor acceptability due to a sand/oily feel in the mouth. Additionally, it needs a vehicle for reconstitution to be supplied along with the microcapsules.

It is evident that there is a commercial need for a pharmaceutical dosage form that effectively provides taste masking, without alteration of the release profile. The prior art fails to describe a pharmaceutical composition with a taste masking coating that provides for immediate release of the encapsulated active ingredient in solution, without the problems of leaching or swelling when exposed to an aqueous media in suspension at the typical pH of saliva.
Summary of the Invention

In one general aspect there is provided a taste masked pharmaceutical composition that includes a core and a taste masking coating. The core includes a therapeutically effective amount of an active pharmaceutical ingredient. The taste masking coating includes at least one polymeric film forming binder and at least one inorganic carrier.

Embodiments of the composition may include one or more of the following features. For example, the active pharmaceutical ingredient may be one or more of antibiotics, antihistamines, antiarthritics, anti psychotics, tranquillizers, antidiabetics, antipyretics, antiulcerants, antiasthmatics, antihypertensives, antianxiety, nonsteroidal anti-inflammatory active ingredients and salts thereof. The active pharmaceutical ingredient may be one or more of clarithromycin, ciprofloxacin, acetaminophen, bambuterol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxicillin, erythromycin, chlorpheniramine, cefuroxime and salts thereof. The active pharmaceutical ingredient may be present in the range of from about 5% w/w to about 90% w/w.

The polymeric film forming binder may be one or more of methacrylic acid ester copolymer, poly (ethyl acrylate-co-methyl methacrylate), amino methacrylic acid ester copolymers, ethyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate. The polymeric film forming binder may be present at a concentration ranging from about 10% w/w to about 90% w/w.

The inorganic carrier may be one or more of calcium carbonate, dibasic calcium phosphate, calcium silicate, magnesium carbonate, magnesium silicate, calcium oxide and magnesium oxide. The inorganic carrier may be present at a concentration ranging from about 1% w/w to about 90% w/w. The ratio of the polymeric film forming binder to the inorganic carrier may range from about 40:60 to about 50:50.

The composition may further include one or more pharmaceutically acceptable excipients.

In another general aspect there is provided a process for the preparation of an oral taste masked composition. The process includes forming a core comprising an active pharmaceutical ingredient; forming a taste masking coating by mixing a polymeric film forming binder and an inorganic carrier; and spraying the taste masking coating on the core to obtain said oral taste masked composition.
Embodiments of the process may include one or more of the following features. For example, the active pharmaceutical ingredient may be one or more of antibiotics, antihistamines, antiarthritics, anti psychotics, tranquillizers, antidiabetics, antipyretics, antiulcerants, antiasthmatics, antihypertensives, antianxiety, nonsteroidal anti-inflammatory active ingredients and salts thereof. The active pharmaceutical ingredient may be one or more of clarithromycin, ciprofloxacin, acetaminophen, bamputerol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxicillin, erythromycin, chlorpheniramine, cefuroxime and salts thereof. The active pharmaceutical ingredient may be present in a range of from about 5% w/w to about 90% w/w.

The polymeric film forming binder may be one or more of methacrylic acid ester copolymer, poly (ethyl acrylate-co-methyl methacrylate), amino methacrylic acid ester copolymers, ethyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthlate and hydroxypropyl methylcellulose phthalate. The polymeric film forming binder may be present at a concentration ranging from about 1% w/w to about 90% w/w.

The inorganic carrier may be one or more of calcium carbonate, dibasic calcium phosphate, calcium silicate, magnesium carbonate, magnesium silicate, calcium oxide and magnesium oxide. The inorganic carrier may be present at a concentration ranging from about 1% w/w to about 90% w/w. The ratio of the film forming binder to the inorganic carrier may range from about 10:90 to about 90:10. The ratio of polymeric film forming binder to inorganic carrier may further range from about 40:60 to about 50:50. The taste masking coating may be about 10% w/w to about 100% w/w of the core.

The process may further include using one or more pharmaceutically acceptable excipients in the dosage form.

In another general aspect there is provided a method of treating a condition for which an active pharmaceutical ingredient is prescribed. The method includes administering a taste masked pharmaceutical composition that includes a core and a taste masking coating. The core includes a therapeutically effective amount of the active pharmaceutical ingredient. The taste masking coating includes at least one polymeric film forming binder and at least one inorganic carrier.

Embodiments of the method may include one or more of the following features or the features described above. For example, the active pharmaceutical ingredient may be
one or more of antibiotics, antihistamines, antiarthritis, anti psychotics, tranquilizers, antidiabetics, antipyretics, antiulcerants, antiasthmatics, antihypertensives, antianxiety, nonsteroidal anti-inflammatory active ingredients and salts thereof. The active pharmaceutical ingredient may be one or more of clarithromycin, ciprofloxacin, acetaminophen, bambuterol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxicillin, erythromycin, chlorpheniramine, cefuroxime and salts thereof.

The details of various embodiments of the inventions are set forth in the accompanying description below. Other features and advantages of the inventions will be apparent from the description and the claims.

**Detailed Description of the Invention**

The oral taste masked compositions described herein include a pharmaceutically effective amount of an active ingredient microencapsulated with a coating which is insoluble or non-swellable in the pH range that exists in the mouth. The coating includes a polymeric film forming binder and a non polymeric, inorganic carrier. The compositions release the contents immediately in the acidic/weakly acidic pH of the stomach. Furthermore, the coating may simply be of a character that will not release active agents in the limited amount of fluid that exists in the mouth/suspending media. After the microcapsules are swallowed, the low pH environment of the stomach and/or simply the large volume of aqueous fluid will dissolve or swell the coating and allow the encapsulated active ingredient to be released immediately (within a period of about one hour). However, other suitable release profiles which provide controlled, delayed, or pulsed release, based on the active ingredient used, will be considered to be within the scope of the present invention.

The therapeutically effective, active pharmaceutical ingredient as described herein is any active ingredient having disagreeable taste or flavor or that produces any sort of local irritation. The active ingredient may be pharmacologically or chemotherapeutically active itself, or may be converted into a pharmacologically or chemotherapeutically active species by a chemical or enzymatic process in the body.

Suitable active pharmaceutical ingredients include one or more of antiallergic, anti-inflammatory, antibacterial, antiasthmatics, nonsteroidal anti-inflammatory, antiarthritic, antipsychotics, tranquilizers, antidiabetics, antipyretics, antiulcerants, prokinetics,
antihypertensives, antianxiety, and nonsteroidal anti-inflammatory active pharmaceutical ingredients and the like.

For example, the active pharmaceutical ingredients may include one or more of antibiotics, such as clarithromycin, ciprofloxacin, cefuroxime axetil, cefpodoxime proxetil, amoxicillin, cefadroxil, moxifloxacin, gatifloxacin and the like; antidiabetics, such as rosiglitazone, pioglitazone, metformin, repaglinide, gliclazide, glibenclamide and the like; antiulcerants, such as ranitidine, cimetidine, famotidine and the like; prokinetics, such as domperidone, cisapride, ondansetron, mosapride and the like; antipyretics, such as paracetamol, aspirin and the like; anti-arthritis, such as rofecoxib, celecoxib, valdecoxib, nimesulide and the like; nonsteroidal anti-inflammatoryys, such as paroxicam, meloxicam, diclofenac, ibuprofen and the like; antiallergics, such as chlorphenramine, diphenhydramine, ceterizine, loratadine, desloratadine, fexofenadine and the like; antiasthmatics, such as montelukast, zafirlukast, bambuterol, pranlukast, salbutamol and the like; antipsychotics, such as alprazolam, fluoxetine, olanzapine, risperidone and the like; and active ingredients used for the treatment of erectile dysfunction, such as sildenafil citrate and the like.

The active ingredient or its pharmaceutically acceptable salt or ester may be used and will be considered to be within the scope of the invention. The active ingredient may be present in the range of about 5% w/w to about 90% w/w of the oral taste masked composition.

Suitable film forming polymeric binders include polymeric substances having sufficient elasticity and structural stability as a film. The film forming polymeric binder is utilized to enhance the film forming properties of the inorganic non polymeric carriers, which either have poor or no film forming properties.

One preferred film forming binder includes the class of the polymethacrylic acid ester copolymers, and more particularly a neutral polymethacrylic acid ester copolymer. Nonetheless, any other insoluble polymer may be considered suitable depending on the type of release profile sought. In one preferred embodiment of the present invention, an immediate release dosage form, a preferred film forming binder is poly (ethyl acrylate-co-methyl methacrylate) available under the trade name Eudragit NE 30 D as a 30% aqueous dispersion. Eudragit NE 30 D has an elongation of 600% and a minimum film forming temperature of less than room temperature. Properties, such as low glass transition
temperature, better film adhesion, and high film, make the use of methacrylic acid copolymers, particularly Eudragit NE 30 D, preferable.

Other suitable film forming polymeric binders include one or more of cellulose ethers, such as ethyl cellulose, hydroxypropyl methyl cellulose, cellulose esters, such as cellulose acetate, polymers exhibiting pH dependent solubility such as cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, Eudragit E, Eudragit L & Eudragit S, and amino methacrylic acid ester copolymers, such as Eudragit RL, Eudragit RS, Eudragit RD and combination thereof.

The concentration range of the film forming binders may be from about 10% to about 90%, preferably from about 10% to about 60%, and more preferably from about 10% to about 40% of the total weight of the taste masked pharmaceutical composition.

The inorganic carriers of the present invention exhibit pH dependent solubility. Suitable inorganic carrier may include one or more of calcium carbonate, dibasic calcium phosphate, calcium silicate, magnesium carbonate, magnesium silicate, calcium oxide, magnesium oxide or a combination thereof. Inorganic carriers, such as calcium carbonate, are practically insoluble in water at a neutral pH. Thus, they maintain sufficient stability against leaching in an aqueous media, but are soluble at a pH range of 1 to 5. They exhibit the highest solubility in an acidic pH of 1 to 2 which results in instantaneous channel formation and the subsequent release of active ingredient.

Suitable concentrations of the inorganic carrier range from about 1% to about 90% of the composition. The ratio of the polymeric film forming binder and inorganic carrier may be varied depending on the type of release profile desired. The polymeric film forming binder and inorganic carrier may have a weight ratio in the range of about 10:90 to about 90:10, preferably from about 70:30 to about 30:70, and even more preferably from about 40:60 to about 50:50.

The blend of the polymeric film forming binder and inorganic carrier renders the taste masking coating completely insoluble and non-swellable in a neutral pH. This characteristic makes them more suitable for use in an aqueous suspension and overcomes the inconvenience of supplying a special vehicle for reconstitution, such as in an oil. The present inventions specifically make use of the aqueous-based coating systems that are safe and make environmental regulatory compliance (e.g., EPA) relatively easy compared to non-aqueous based coating systems.
Although there is no limitation to the type of water insoluble polymer used, the neutral methacrylic acid ester copolymers were found especially suitable because of their balanced permeability characteristics and hydropilicity. Accordingly, any polymer having similar permeability characteristics will be deemed useful for the invention. Insoluble polymers, such as ethyl cellulose, form films having good physical stability, however, their poor permeability delays the release of the poorly water-soluble active ingredients because the hydrophobicity reduces the exposure of the inorganic carrier to the microenvironment. This in turn limits channel formation, which delays active pharmaceutical ingredient release.

According to the invention the process for the preparation of an oral taste masked composition generally includes;

a) mixing a polymeric film forming binder ranging from 1% w/w to 90% w/w and non polymeric inorganic carrier ranging from 1% w/w to 90% w/w, wherein the ratio of the film forming binder and the non polymeric inorganic carrier ranges from 10:90 to 90:10, to obtain a taste masking coating, and

b) spraying the taste masking coating on a core that includes active ingredient in the range of 5% w/w to 90% w/w, the taste masking coating forming 10% to 100% of weight of the total weight of the core, to obtain the oral tasted masked composition.

The following examples further exemplify the inventions and are not intended to limit the scope of the inventions.

**Example 1**

Ciprofloxacin Hydrochloride Microcapsules.

**Core composition:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin Hydrochloride</td>
<td>600 gm</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>100 gm</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>40 gm</td>
</tr>
<tr>
<td>Purified water</td>
<td>200 ml</td>
</tr>
</tbody>
</table>

**Coating composition:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin HCl cores (#40/60)</td>
<td>150 gm</td>
</tr>
<tr>
<td>Eudragit NE 30 D</td>
<td>150 gm</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>105 gm</td>
</tr>
<tr>
<td>Purified water</td>
<td>300 ml</td>
</tr>
</tbody>
</table>
Procedure:

Procedure for forming the core:

Ciprofloxacin Hydrochloride and Microcrystalline Cellulose were mixed in a rapid mixer granulator for 10 minutes and then the mixture was granulated with Polyvinylpyrrolidone solution until the wet mass formed the required consistency. The granulator was operated at a slow speed to obtain granules. The granules were dried at 60°C and the preferred particle size fraction was collected for taste masking coating.

Procedure for coating the core:

The granules were charged in the material chamber of a fluidized bed coater (GPCG1) and the coating parameters were set. The coating dispersion was sprayed until the effective taste masking was achieved. The samples were removed at 70% and 100% coating levels to study the dissolution profile.

The following coating parameters were selected for coating of the core:

Inlets temperature – 55°C to 65°C, exhaust temperature - 25°C to 35°C, spray rate – 15 to 20 gm/min, height of partition chamber – 15 mm, distribution plate – B, atomization - 2.25 kg/cm², inlet airflow rate – 1.8 to 2.5

Table 1

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coating – 70% (Microcapsules)</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>10</td>
<td>25.15</td>
</tr>
<tr>
<td>2.</td>
<td>20</td>
<td>52.62</td>
</tr>
<tr>
<td>3.</td>
<td>30</td>
<td>74.97</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>89.41</td>
</tr>
<tr>
<td>5.</td>
<td>60</td>
<td>89.95</td>
</tr>
</tbody>
</table>
### Table 2

Dissolution of Ciprofloxacin Hydrochloride Microcapsules (pH 4)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Coating – 70% (Microcapsules)</td>
</tr>
<tr>
<td>1.</td>
<td>10</td>
<td>7.49</td>
</tr>
<tr>
<td>2.</td>
<td>20</td>
<td>22.81</td>
</tr>
<tr>
<td>3.</td>
<td>30</td>
<td>36.46</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>57.31</td>
</tr>
<tr>
<td>5.</td>
<td>60</td>
<td>73.07</td>
</tr>
</tbody>
</table>

### Table 3

Dissolution of the Ciprofloxacin Hydrochloride microcapsules in water (900 ml).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution in water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Coating – 70% (Microcapsules)</td>
</tr>
<tr>
<td>1.</td>
<td>10</td>
<td>0.80</td>
</tr>
<tr>
<td>2.</td>
<td>20</td>
<td>1.50</td>
</tr>
<tr>
<td>3.</td>
<td>30</td>
<td>3.90</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>4.19</td>
</tr>
<tr>
<td>5.</td>
<td>60</td>
<td>4.80</td>
</tr>
</tbody>
</table>

### Example 2

Rapidly Disintegrating Tablets of Ciprofloxacin Hydrochloride

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ingredients</th>
<th>Amount/tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ciprofloxacin Hydrochloride (As microcapsules – 70% build up)</td>
<td>125.0</td>
</tr>
<tr>
<td>2</td>
<td>Mannitol (Pearlitol SD 200)</td>
<td>385.0</td>
</tr>
<tr>
<td>3</td>
<td>Crospovidone XL-10</td>
<td>35.0</td>
</tr>
<tr>
<td>4</td>
<td>Aspartame</td>
<td>6.0</td>
</tr>
<tr>
<td>5</td>
<td>Pineapple flavour</td>
<td>6.0</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium Stearate</td>
<td>6.0</td>
</tr>
<tr>
<td>7</td>
<td>Colloidal silicone dioxide</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Procedure:

All of the ingredients, except the magnesium stearate, were mixed in a double cone blender for 10 minutes. The granular blend was then lubricated with magnesium stearate and compressed using suitable parameters. The coating composition is the same as described above in Example 1.

Table 4

Dissolution of Ciprofloxacin Hydrochloride Rapidly disintegrating Tablets.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>10</td>
<td>22.78</td>
</tr>
<tr>
<td>2.</td>
<td>20</td>
<td>46.86</td>
</tr>
<tr>
<td>3.</td>
<td>30</td>
<td>70.36</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>88.53</td>
</tr>
<tr>
<td>5.</td>
<td>60</td>
<td>93.41</td>
</tr>
</tbody>
</table>

Example 3

Ciprofloxacin base microcapsules.

Core Composition:
Ciprofloxacin base 500 gm
Microcrystalline Cellulose 100 gm
Polyvinylpyrrolidone K-30 40 gm
Purified water 300 ml

Coating Composition:
Ciprofloxacin base cores (#40/60) 150 gm
Eudragit NE 30 D 105 gm
Calcium Carbonate 73.5 gm
Purified water 210 ml
### Table 5
Dissolution of Ciprofloxacin Microcapsules.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Coating – 70% (Microcapsules)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>83.61</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>91.10</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>89.29</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>89.38</td>
</tr>
</tbody>
</table>

### Table 6
Dissolution of Ciprofloxacin Microcapsules.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Coating – 100% (Microcapsules)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>71.73</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>97.13</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>97.67</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>95.58</td>
</tr>
</tbody>
</table>

### Table 7
Comparative dissolution of ciprofloxacin microcapsules at different ratios of Eudragit NE 30 D (NE) and Calcium Carbonate (CC).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Time in minutes</th>
<th>% Dissolution at pH 1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(NE:CC = 40:60) (*Build up – 40%)</td>
</tr>
<tr>
<td>1.</td>
<td>10</td>
<td>25.29</td>
</tr>
<tr>
<td>2.</td>
<td>20</td>
<td>49.15</td>
</tr>
<tr>
<td>3.</td>
<td>30</td>
<td>70.53</td>
</tr>
<tr>
<td>4.</td>
<td>45</td>
<td>82.52</td>
</tr>
<tr>
<td>5.</td>
<td>60</td>
<td>92.51</td>
</tr>
</tbody>
</table>

* The build up found to be reasonably sufficient for the effective taste masking.
Example 4
Ciprofloxacin for oral suspension

Ciprofloxacin base (below # 60) 125 mg
(As microcapsules from Example 3)
5 Xanthan Gum 25.0 mg
Aspartame 5.0 mg
Pharma Sugar (#100) 2.0 gm
Titanium dioxide 10.0 mg
Sodium benzoate 10.0 mg

The suspension was reconstituted with boiled and cooled water and evaluated for taste and physical changes; the data is depicted in Table 8.

Table 8
Taste masking studies of Ciprofloxacin Oral suspension

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Day of evaluation</th>
<th>Taste</th>
<th>Resuspendability</th>
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<tr>
<td>5.</td>
<td>Day 5</td>
<td>No bitterness</td>
<td>No cake formation</td>
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Example 5
Taste Masked Controlled Release Ciprofloxacin HCl Microcapsules

Procedure:
The cores of Example 1 were used for the controlled release coating of the following composition. Significant sustained effect was achieved at a coating build up of approximately 60%.

Ciprofloxacin base cores 150.0 gm
(As per Example 1)
Aquacoat ECD 30% 200 gm
Calcium carbonate 90 gm
Purified water 250 ml
Surprisingly, by replacing the Eudragit NE 30 D with an equivalent or lesser amount of ethylcellulose, the release profile becomes one of sustained release behavior.

**Example 6**

Taste Masked Microcapsules of Bambuterol.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose spheres</td>
<td>150 gm</td>
</tr>
<tr>
<td>(Celphere, FMC)</td>
<td></td>
</tr>
<tr>
<td>Active ingredient coating</td>
<td></td>
</tr>
<tr>
<td>Bambuterol Hydrochloride</td>
<td>40.0 gm</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (5 cps)</td>
<td>10.0 gm</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>20 ml</td>
</tr>
<tr>
<td>D.M. Water</td>
<td>130 ml</td>
</tr>
</tbody>
</table>

Taste masking coating

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient layered microcapsules</td>
<td>150 gm</td>
</tr>
<tr>
<td>Eudragit NE 30 D</td>
<td>75 gm</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>52.5 gm</td>
</tr>
</tbody>
</table>

**Procedure:**

The active ingredient suspension was layered on the microcrystalline cellulose spheres using a fluidized bed coating. Then the active ingredient-layered microcapsules were further coated with the taste masking coating as described above. Complete taste masking was achieved at approximately 50% to 60% build up. The process used was the same as described above with respect to Example 1.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention.

Accordingly, it is not intended that the invention be limited, except as by the appended claims.
We Claim:

1. A taste masked pharmaceutical composition comprising:
   a core comprising a therapeutically effective amount of an active pharmaceutical
   ingredient; and
   a taste masking coating,
   wherein the taste masking coating comprises at least one polymeric film forming
   binder and at least one inorganic carrier.

2. The composition according to claim 1, wherein the active pharmaceutical
   ingredient comprises one or more of antibiotics, antihistamines, antiarthritis, anti
   psychotics, tranquilizers, antidiabetics, antipyretics, antiulcerants, antiasthmatics,
   antihypertensives, antianxiety, nonsteroidal anti-inflammatory active ingredients
   and salts thereof.

3. The composition according to claim 1, wherein the active pharmaceutical
   ingredient comprises one or more of clarithromycin, ciprofloxacin, acetaminophen,
   bambuterol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxycillin,
   erythromycin, chlorpheniramine, cefuroxime and salts thereof.

4. The composition according to claim 1, wherein the active pharmaceutical
   ingredient is present in the range of from about 5% w/w to about 90% w/w.

5. The composition according to claim 1, wherein the polymeric film forming binder
   comprises one or more of methacrylic acid ester copolymer, poly (ethyl acrylate-
   co-methyl methacrylate), amino methacrylic acid ester copolymers, ethyl cellulose,
   hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate and
   hydroxypropyl methylcellulose phthalate.

6. The composition according to claim 5, wherein the polymeric film forming binder
   is present at a concentration ranging from about 10% w/w to about 90% w/w.

7. The composition according to claim 1, wherein the inorganic carrier comprises one
   or more of calcium carbonate, dibasic calcium phosphate, calcium silicate,
   magnesium carbonate, magnesium silicate, calcium oxide and magnesium oxide.

8. The composition according to claim 7, wherein the inorganic carrier is present at a
   concentration ranging from about 1% w/w to about 90% w/w.
9. The composition according to claim 1, wherein the ratio of the polymeric film forming binder to the inorganic carrier ranges from about 40:60 to about 50:50.

10. The composition according to claim 1, further comprising one or more pharmaceutically acceptable excipients.

11. A process for the preparation of an oral taste masked composition, the process comprising:

forming a core comprising an active pharmaceutical ingredient;

forming a taste masking coating by mixing a polymeric film forming binder and an inorganic carrier; and

spraying the taste masking coating on the core to obtain said oral taste masked composition.

12. The process according to claim 11, wherein the active pharmaceutical ingredient comprises one or more of antibiotics, antihistamines, antiarthritis, anti psychotics, tranquillizers, antidiabetics, antipyretics, antiulcerants, antiasthematics, antihypertensives, anti anxiety, nonsteroidal anti-inflammatory active ingredients and salts thereof.

13. The process according to claim 11, wherein the active pharmaceutical ingredient comprises one or more of clarithromycin, ciprofloxacin, acetaminophen, bambuterol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxycillin, erythromycin, chlorpheniramine, cefuroxime and salts thereof.

14. The process according to claim 11, wherein the active pharmaceutical ingredient is present in a range of from about 5% w/w to about 90% w/w.

15. The process according to claim 11, wherein the polymeric film forming binder comprises one or more of methacrylic acid ester copolymer, poly (ethyl acrylate-co-methyl methacrylate), amino methacrylic acid ester copolymers, ethyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate.

16. The process according to claim 11, wherein the polymeric film forming binder is present at a concentration ranging from about 1% w/w to about 90% w/w.
17. The process according to claim 11, wherein the inorganic carrier comprises one or more of calcium carbonate, dibasic calcium phosphate, calcium silicate, magnesium carbonate, magnesium silicate, calcium oxide and magnesium oxide.

18. The process according to claim 11, wherein the inorganic carrier is present at a concentration ranging from about 1% w/w to about 90% w/w.

19. The process according to claim 11, wherein the ratio of the film forming binder to the inorganic carrier ranges from about 10:90 to about 90:10.

20. The process according to claim 11, wherein the ratio of polymeric film forming binder to inorganic carrier ranges from about 40:60 to about 50:50.

21. The process according to claim 11, wherein the taste masking coating comprises about 10% w/w to about 100% w/w of the core.

22. The process according to claim 11, further comprising one or more pharmaceutically acceptable excipients.

23. A method of treating a condition for which an active pharmaceutical ingredient is prescribed, the method comprising administering a taste masked pharmaceutical composition comprising:

   a core comprising a therapeutically effective amount of the active pharmaceutical ingredient; and
   a taste masking coating,

wherein the taste masking coating comprises at least one polymeric film forming binder and at least one inorganic carrier.

24. The method according to claim 23, wherein the active pharmaceutical ingredient comprises one or more of antibiotics, antihistamines, antiarthritics, anti psychotics, tranquillizers, antidiabetics, antipyretics, antiulcerants, antiasthmatics, antihypertensives, antianxiety, nonsteroidal anti-inflammatory active ingredients and salts thereof.

25. The method according to claim 23, wherein the active pharmaceutical ingredient comprises one or more of clarithromycin, ciprofloxacin, acetaminophen, bumbuterol, olanzapine, ranitidine, sildenafil, cefpodoxime, amoxycillin, erythromycin, chlorpheniramine, cefuroxime and salts thereof.
# INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61K9/28

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>
| X        | EP 0 914 823 A (LANNACHER HEILMITTEL)  
12 May 1999 (1999-05-12)  
abstract  
paragraph '0009!'  
example 1  
claims 4,6 | 1-25 |
| X        | WO 01/80829 A (SQUIBB BRISTOL MYERS CO)  
1 November 2001 (2001-11-01)  
abstract  
page 2, lines 14-22  
page 4, lines 8-11  
page 5, lines 14-19  
page 11, lines 17-20  
page 12, lines 4-10  
exa... | 1-25 |

Further documents are listed in the continuation of box C.  
Patent family members are listed in annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  *A* document member of the same patent family

**Date of the actual completion of the international search**  
1 September 2004

**Date of mailing of the international search report**  
09/09/2004

**Name and mailing address of the ISA**  
European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 940-2040, Tx. 31 651 epo nl,  
FAX (+31-70) 940-3016

**Authorized officer**  
Villa Riva, A
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<tr>
<td>A</td>
<td>EP 1 157 690 A (PHARMA PASS LLC) 28 November 2001 (2001-11-28) abstract; example 2</td>
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<tr>
<td>A</td>
<td>US 4 670 459 A (SJOERDSMA ALBERT) 2 June 1987 (1987-06-02) example 1</td>
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</table>
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 23-25 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.
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<th>Patent family member(s)</th>
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<td>AU 5550901 A</td>
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