Title: EXTENDED RELEASE TABLETS OF CLARITHROMYCIN

Abstract: The present invention relates to extended release tablets for oral administration comprising clarithromycin and a pharmaceutically acceptable carrier, and processes for their preparation.
EXTENDED RELEASE TABLETS OF CLARITHROMYCIN

Field of the Invention

The present invention relates to extended release tablets for oral administration comprising clarithromycin and a pharmaceutically acceptable carrier, and processes for their preparation.

Background of the Invention

Oral ingestion is one of the primary routes used for drug administration. This route provides a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems there is little or no control over the release of the drug and an effective concentration can only be maintained by repeated administrations. Controlled release systems provide a uniform concentration of drug at the absorption site for an extended period of time and thus, after absorption, allow maintenance of plasma concentrations within a desired therapeutic range. This reduces the frequency of administration.

The advantages of controlled release dosage forms for extended or sustained action are well known. Some of them include a reduced daily dosage, improved patient compliance, prevention of delay in recovery, avoidance of bacterial resistance and ensuring successful therapy. The macrolide antibiotics are known for their anti-bacterial activity against a number of micro-organisms and are typically administered as immediate release (IR) compositions two or three times a day for about 10 to 14 days. Clarithromycin (6-O-methylerythromycin A), in particular, has a very bitter metallic taste which can result in poor compliance of the dosing regimen or selection of another therapeutic agent, possibly making it a less effective therapeutic agent.

An approach to address the possible non-compliance with the regimen is to develop controlled release solid preparations containing erythromycin derivatives. Unfortunately the properties of these macrolides, like many other poorly soluble basic drugs, do not allow them to be incorporated in a single oral dosage form or to provide a controlled efficient release of drug throughout a 24 hr period with reproducible bioavailability. The main reason for this is that erythromycin derivatives are slightly alkaline, practically water insoluble, acid-sensitive drugs. A basic drug's solubility
decreases with an increasing pH as it proceeds distally towards the large intestine (pH 6 to 8). It is soluble in stomach (pH 1.2) and upper or proximal region of small intestine (pH 5). Thus, a poorly soluble basic drug will lead to less drug being available for absorption in the lower or distal intestine. Moreover, a daily dose of 500-1000 mg of clarithromycin has to be incorporated in a relatively small matrix in order to allow for swallowing; this leaves relatively little room for optimization of the biopharmaceutical and physicochemical properties of a formulation.

**Summary of the Invention**

In one general aspect there is provided an extended release tablet of clarithromycin for oral administration. The extended release tablet includes clarithromycin and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier includes a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the clarithromycin may be between about 50% to about 75% w/w of the total tablet weight and the pharmaceutically acceptable carrier may be present from about 20% to about 30% w/w of the total tablet weight.

The lactose includes one or more of anhydrous lactose, spray-dried lactose and lactose monohydrate.

The extended release tablet may further include one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients. The rate-controlling polymers may be one or more of carbohydrate gums, polyuronic acid salts, cellulose ethers, acrylic acid polymers and mixtures thereof. The carbohydrate gums may be one or more of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan and locust bean gum. The polyuronic acid salts may be one or more of sodium alginate, potassium alginate and ammonium alginate. The cellulose ethers may be one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose and hydroxyethyl cellulose. The acrylic polymer may be one or both of polyacrylic polymer and carboxy vinyl polymer. The rate controlling polymers may be present from about 0.1% to about 4.5% w/w of total tablet weight.
The pharmaceutically acceptable excipients may be one or more of binders, lubricants, glidants, colorants and flavoring agents.

The binders may be one or more of starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose, polyvinyl pyrrolidone and hydroxypropyl cellulose.

The lubricants may be one or more of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate.

The glidants may be one or both of colloidal silicon dioxide and talc.

The extended release tablet may further include one or more of omeprazole, metronidazole, amoxicillin, rifampicin, lansoprazole, ciprofloxacin, ethambutol and ritonavir.

In another general aspect there is provided a process for the preparation of extended release tablets of clarithromycin for oral administration. The process includes blending clarithromycin, a pharmaceutically acceptable carrier, one or more rate-controlling polymers and one or more binders to form a blend; screening the blend; lubricating the blend; compressing the blend to form tablets; and optionally coating the tablets. The pharmaceutically acceptable carrier comprises a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

In another general aspect there is provided process for the preparation of extended release tablets of clarithromycin for oral administration. The process includes blending clarithromycin, a pharmaceutically acceptable carrier, one or more rate-controlling polymers and one or more binders to form a blend; compacting the blend to form granules; sizing the granules; lubricating the granules; compressing to form tablets; and optionally coating the tablets. The pharmaceutically acceptable carrier comprises a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

Embellishments of the process may include one or more of the following features. For example, the granulation technique used may be wet or dry granulation.

In another general aspect there is provided a method of treatment for bacterial infections in a mammal in need of treatment. The method includes administering an extended release tablet of clarithromycin that includes clarithromycin and a
pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier includes a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

Embodiments of the method may include one or more of the following features. For example, the extend release tablet may further include one or more of omeprazole, metronidazole, amoxicillin, rifampicin, lansoprazole, ciprofloxacin, ethambutol and ritonavir.

Detailed Description of the Invention

The inventors have surprisingly now formulated extended release tablets of clarithromycin. The tablets include clarithromycin, one or more rate-controlling polymers and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier includes a mixture of lactose and microcrystalline cellulose in a ratio ranging from about 3:1 to about 1:3.

Various ratios of lactose and microcrystalline cellulose may be employed for preparing tablets, such as about 1.5 to about 1, about 2.3 to about 1, about 3 to about 1 and about 1 to about 3. Tablets containing only lactose were also prepared and it was found that these tablets exhibited significantly higher C_{max} (peak plasma concentration).

Solid dosage forms, the most commonly used method of drug delivery, have seen an increasing sophistication in terms of functionality of the excipients. The transformation of excipients from inert ingredients to functional components has occurred. It is recognized that excipients are critical for stability, safety and performance of the dosage forms. In the present invention, the importance of the ratio in which the two diluents or fillers, lactose and microcrystalline cellulose are added, is emphasized. It is demonstrated that the ratio has a significant effect on the bioavailability of the tablets and the ratio ranging from about 3 to about 1 and from about 1 to about 3 exhibits extended release.

Suitable lactose includes one or more of anhydrous lactose, spray-dried lactose and lactose monohydrate. For example, lactose monohydrate may be used.

Microcrystalline cellulose revolutionized tabletting because of its unique compressibility and carrying capacity. It exhibits excellent properties as an excipient for solid dosage forms. It has a high binding capability and creates tablets that are extremely hard, stable, yet disintegrate rapidly. Other advantages include low friability, inherent
lubricity, and the highest dilution potential of all binders. These properties make microcrystalline cellulose particularly valuable as a filler and binder for formulations prepared by direct compression, although it is also used in wet or dry granulation. It is commercially available under the tradename EMCOCEL™ from Edward Mendell Co., Inc. and as Avicel™ from FMC Corp.

The pharmaceutically acceptable carrier, which includes lactose and microcrystalline cellulose, may be present at from about 20% to about 30% w/w of the total tablet weight.

Suitable rate-controlling polymers of the extended release tablets include one or more of carbohydrate gum, polyuronic acid salts, cellulose ethers, acrylic acid polymers and mixtures, thereof. Suitable carbohydrate gums include one or more of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan, locust bean gum and other carbohydrate gums having similar properties. Suitable polyuronic acid salts include one or more of alkali metal salts of alginic acid or pectic acid and mixtures thereof. Suitable alkali metal salts of alginic acid that may be used include one or more of sodium alginate, potassium alginate, ammonium alginate and other suitable alkali metal salts of alginic acid. Suitable cellulose ethers include one or more of hydroxypropyl methyl cellulose, hydroxypropyl cellulose and other suitable cellulose ethers. Suitable acrylic acid polymers include any suitable polyacrylic acid polymers or carboxyvinyl polymers such as those available under the brand name carbopol.

The one or more rate-controlling polymers may be present at a concentration from about 0.1% to about 4.5% w/w of the total tablet weight.

In addition to the active, pharmaceutically acceptable carrier and one or more rate-controlling polymers, the extended release tablets may additionally contain one or more pharmaceutically acceptable excipients including one or more of binders, lubricants, glidants, colorants and flavoring agents.

Suitable binders include one or more of starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose, polyvinyl pyrrolidone, polyethylene glycols, polyvinyl acetate and hydroxypropyl cellulose.
Suitable lubricants include one or more of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate.

Suitable glidants include colloidal silicon dioxide (aerosil) or talc.

Suitable coloring or flavoring agents include those approved for use by the United States Food and Drug Administration (FDA) and are well known to those skilled in the art.

Also provided is a process for the preparation of extended release tablets of clarithromycin that include clarithromycin and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier includes a mixture of lactose and microcrystalline cellulose in a ratio ranging from about 3:1 to about 1:3.

The tablets may be prepared by direct compression. The clarithromycin may be blended with one or more rate-controlling polymers and a pharmaceutically acceptable carrier which includes a mixture of lactose and microcrystalline cellulose and one or more pharmaceutically acceptable excipients. This blend is screened and compressed after lubrication.

The tablets may also be prepared by wet granulation or dry granulation. The clarithromycin may be blended with one or more rate-controlling polymers and a pharmaceutically acceptable carrier which includes a mixture of lactose and microcrystalline cellulose and one or more pharmaceutically acceptable excipients. This blend is then granulated with a suitable binder solution to obtain granules. The granules are further lubricated and compressed.

In one embodiment, the process of preparing the extended release tablets of clarithromycin includes blending clarithromycin, a pharmaceutically acceptable carrier, which includes lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3, one or more rate-controlling polymers and one or more binders; screening the blend; lubricating the blend; compressing the blend to form tablets; and optionally coating the tablets.

In another embodiment, the process of preparing the extended release tablets of clarithromycin includes blending clarithromycin, a pharmaceutically acceptable carrier, which includes lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.
and one or more rate-controlling polymers; compacting the blend, screening into granules; lubricating the granules; compressing to form tablets; and optionally coating the tablets.

In another embodiment, the process of preparing the extended release tablets of clarithromycin includes blending clarithromycin, a pharmaceutically acceptable carrier, which includes lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3 and one or more rate-controlling polymers; granulating the blend with a solution of binder; drying the granules, screening the granules, lubricating the granules; compressing the granules to form tablets; and optionally coating the tablets.

Also provided is a method of treating a bacterial infection. The method includes administering extended release tablets of clarithromycin which include clarithromycin and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier includes a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

The method of treating may further include concurrently administering one or more of omeprazole, metronidazole, amoxicillin, rifampicin, lansoprazole, ciprofloxacin, ethambutol, and ritonavir with clarithromycin.

The following examples are provided to illustrate various implementations of the invention and are not intended to limit it.
### EXAMPLES 1-5

#### Preparation of extended release tablets of Clarithromycin

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ingredients</th>
<th>Percent w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ex-1</td>
</tr>
<tr>
<td>1</td>
<td>Clarithromycin</td>
<td>61.5</td>
</tr>
<tr>
<td>2</td>
<td>Hydroxypropyl methylcellulose</td>
<td>4.2</td>
</tr>
<tr>
<td>3</td>
<td>Lactose</td>
<td>6.5</td>
</tr>
<tr>
<td>4</td>
<td>Microcrystalline cellulose</td>
<td>19.5</td>
</tr>
<tr>
<td>5</td>
<td>Polyvinylpyrrolidone</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>Sodium Stearyl Fumarate</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>Talc</td>
<td>1.8</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium Stearate</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>Colloidal silicon dioxide</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>Opadry</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td><strong>Ratio of lactose and microcrystalline cellulose</strong></td>
<td>1:3</td>
</tr>
</tbody>
</table>

**Procedure:**

Clarithromycin, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, microcrystalline cellulose and lactose were sieved through a British Standard Sieve (BSS) 18 mesh sieve, blended together and granulated with binder solution. The resulting granulate was dried in a fluid bed drier. The dried granules were sized and lubricated with the remaining ingredients and compressed to form tablets. The tablets were coated with opadry dispersion.

**Pharmacokinetics**

A single dose bioavailability study was conducted under a fasting state to determine the concentration - time plasma profile on 20 healthy subjects. Clarithromycin ER tablets 500 mg prepared according to Examples 3 and 4 were compared with clarithromycin extended release 500 mg tablets (Biaxin XL tablets manufactured by


Abbott Laboratories, USA and Klaricid XL tablets manufactured by Abbott Laboratories, UK). There was a washout period of 3 days.

Values for pharmacokinetic parameters, including observed $C_{\text{max}}$, AUC$_{(0-t)}$ and AUC$_{(0-\infty)}$, were calculated using standard non-compartmental methods. The results as indicated by ratio of test to reference are shown in Table 1.

**Table 1: Summary of pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>AUC$_{(0-t)}$ (ng.hr /ml)</th>
<th>AUC$_{(0-\infty)}$ (ng.hr /ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio % (D/A)</td>
<td>87.68</td>
<td>85.74</td>
<td>85.19</td>
</tr>
<tr>
<td>Ratio % (C/B)</td>
<td>112.04</td>
<td>120.33</td>
<td>121.20</td>
</tr>
</tbody>
</table>

Reference A: Biaxin XL (500 mg) tablets, Mfd. By Abbott Laboratories, USA

Reference B: Klaricid XL (500 mg) tablets, Mfd. By Abbott Laboratories, UK

Test C: Clarithromycin extended release tablets (Example 4)

Test D: Clarithromycin extended release tablets (Example 3)

As is evident from Table 1, clarithromycin ER tablets (formulated as per Examples 3 and 4) are suitable for administration to a patient for extended release.

Similar studies were carried out in which 500 mg clarithromycin ER tablets were prepared according to Example 5.

Values for the pharmacokinetic parameters, including observed $C_{\text{max}}$, AUC$_{(0-t)}$ and AUC$_{(0-\infty)}$, were calculated using standard non-compartmental methods. The results are indicated by the ratio of test to reference are shown in Table 2.

**Table 2: Summary of pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>AUC$_{(0-t)}$ (ng.hr /ml)</th>
<th>AUC$_{(0-\infty)}$ (ng.hr /ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio % (T/R)</td>
<td>161.22</td>
<td>102.82</td>
<td>101.31</td>
</tr>
</tbody>
</table>
Reference R: Biaxin XL (500 mg) tablets, Mfd. By Abbott Laboratories, USA

Test T: Clarithromycin extended release tablets (Example 5)

As evident from Table 2, the tablets prepared with lactose alone exhibited a significantly higher $C_{\text{max}}$.

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. An extended release tablet for oral administration comprising clarithromycin and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

2. The extended release tablet according to claim 1, wherein the clarithromycin comprises from about 50% to about 75% w/w of the total tablet weight.

3. The extended release tablet according to claim 1, wherein the pharmaceutically acceptable carrier comprises from about 20% to about 30% w/w of the total tablet weight.

4. The extended release tablet according to claim 1, wherein the lactose comprises one or more of anhydrous lactose, spray-dried lactose and lactose monohydrate.

5. The extended release tablet according to claim 1, further comprising one or more rate-controlling polymers and one or more pharmaceutically acceptable excipients.

6. The extended release tablet according to claim 5, wherein the rate controlling polymers comprise one or more of carbohydrate gums, polyuronic acid salts, cellulose ethers, acrylic acid polymers and mixtures thereof.

7. The extended release tablet according to claim 6, wherein the carbohydrate gums comprise one or more of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan and locust bean gum.

8. The extended release tablet according to claim 6, wherein the polyuronic acid salts comprise one or more of sodium alginate, potassium alginate and ammonium alginate.

9. The extended release tablet according to claim 6, wherein the cellulose ethers comprise one or more of hydroxypropyl methylcellulose, hydroxy propyl cellulose and hydroxyethyl cellulose.

10. The extended release tablet according to claim 6, wherein the acrylic polymer comprises polyacrylic polymer and carboxy vinyl polymer.

11. The extended release tablet according to claim 5, wherein the rate controlling polymers comprise about 0.1% to about 4.5% w/w of total tablet weight.
12. The extended release tablet according to claim 5, wherein the one or more pharmaceutically acceptable excipients comprise one or more of binders, lubricants, glidants, colorants and flavoring agents.

13. The extended release tablets according to claim 12, wherein the binders comprise one or more of starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose, polyvinyl pyrrolidone and hydroxypropyl cellulose.

14. The extended release tablets according to claim 12 wherein the lubricants comprise one or more of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate.

15. The extended release tablets according to claim 12, wherein the glidants comprise one or both of colloidal silicon dioxide and talc.

16. The extended release tablet of claim 1, further comprising one or more of omeprazole, metronidazole, amoxicillin, rifampicin, lansoprazole, ciprofloxacin, ethambutol and ritonavir.

17. A process for the preparation of extended release tablets of clarithromycin for oral administration, the process comprising:

blending clarithromycin, a pharmaceutically acceptable carrier, one or more rate-controlling polymers and one or more binders to form a blend;

screening the blend;

lubricating the blend;

compressing the blend to form tablets; and

optionally coating the tablets,

wherein the pharmaceutically acceptable carrier comprises a mixture of lactose and microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

18. A process for the preparation of extended release tablets of clarithromycin for oral administration, the process comprising:

blending clarithromycin, a pharmaceutically acceptable carrier, one or more rate-controlling polymers and one or more binders to form a blend;
compacting the blend to form granules;
sizing the granules;
lubricating the granules;
compressing to form tablets; and
optionally coating the tablets;
wherein the pharmaceutically acceptable carrier comprises a mixture of lactose and
microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

19. The process of claim 18, wherein the granulation comprises wet and dry
granulation.

20. A method of treatment for bacterial infections in a mammal in need of
treatment, the method comprising administering an extended release tablet of
clarithromycin comprising clarithromycin and a pharmaceutically acceptable carrier,
wherein the pharmaceutically acceptable carrier comprises a mixture of lactose and
microcrystalline cellulose in a ratio ranging from 3:1 to 1:3.

21. The method according to claim 20, wherein the extend release tablet further
comprises one or more of omeprazole, metronidazole, amoxicillin, rifampicin,
lansoprazole, ciprofloxacin, ethambutol and ritonavir.