

**Title:** IMPROVED PHARMACEUTICAL DENTAL FORMULATIONS

**Abstract:** An improved Pharmaceutical dental gel preparation comprising of metronidazole benzoate, chlorhexidine gluconate, and local anesthetic as the active ingredient; glycol as the solvent medium; a carboxyvinyl polymer as gelling polymer and a copolymer of methyl vinyl ether and maleic anhydride as mucoadhesive agent.
IMPROVED PHARMACEUTICAL DENTAL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to improved pharmaceutical dental formulation for topical application of metronidazole benzoate, chlorhexidine gluconate and local anaesthetic for the treatment of gingivitis and periodontitis where an muco-adhesive agent is employed which facilitates bio adhesion of the gel in periodontal pockets thus releases the drug at required site for longer duration, making it more efficacious.

DESCRIPTION OF THE PRIOR ART

Periodontal disease is a major concern in dentistry. The microorganisms most widely encountered are anaerobes and facultative streptococci. Periodontal disease encompasses specific conditions affecting the gingiva and the supporting connective tissues and alveolar bone. Gingivitis is thought to be caused by a non-specific bacterial plaque flora that gradually changes from predominantly gram positive to more gram negative. Periodontitis, which is associated with gram negative microflora, is always preceded by gingivitis.

Most gingivitis and periodontitis can be prevented and treated by adequate oral hygiene and plaque removal using mechanical means such as toothbrushes. Mechanical removal of calculus is necessary where the build up is significant. The treatment of periodontal disease includes long acting capsules or tablets held in the mouth, buccal implants for releasing drugs into the saliva, topically applied gels, and topically applied drug containing bandages, impregnated or drug releasing forms of dental floss and solid absorbable fibers of polyglycolic acid with therapeutic agents incorporated therein.
In case of site-specific drug delivery for treatment of the periodontal pockets it is necessary to retain the drug near to the affected areas surrounding the teeth so as to facilitate diffusion of the therapeutic agent to the affected site.

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole is reduced by bacterial nitroreductase to an unstable intermediate, which interacts with DNA, effectively preventing further replication.

Metronidazole is bactericidal. Minimum inhibitory concentration (MIC) for susceptible anaerobic bacteria generally ranges from 0.1 to 8μg/ml. It also has activity against the facultative anaerobes Gardnerella vaginalis and Helicobacter pylori and against some spirochetes, several protozoa, anaerobic and gram negative bacteria. Metronidazole benzoate topical formulation when applied to periodontal pockets, comes in contact with gingival cravicular fluid or saliva containing esterases which hydrolyse metronidazole benzoate to free active metronidazole which exerts its activity on anaerobic bacteria present in periodontal region.

The long term administration of oral metronidazole gives rise to side effects such as gastro-intestinal disturbances, nausea, metallic taste, anorexia, vomiting, diarrhoea, dry mouth and glossitis. Thus, to avoid the drawbacks of systemic administration, a dental gel for topical application of metronidazole is desirable in periodontitis.

A dental gel comprising of metronidazole benzoate 25% used for gingivitis and periodontitis and its topical use seems to be as effective as conventional therapy in the treatment of periodontitis. (J. Clin. Period., 1992: 19, 715-729). The use of metronidazole benzoate 25% dental gel is associated with a limitation i.e. when
applied subgingivally, the active agent reaches sulcus for which special injector is required and the procedure is cumbersome and is done by dental surgeon only.

Chlorhexidine is a bis biguanide antiseptic and disinfectant effective against a wide range of bacteria, some fungi and viruses. A dental gel comprising of chlorhexidine is also used for gingivitis and prevention of plaque. A dental composition containing chlorhexidine gluconate is also used in various strengths of 0.1% to 1% in the form of topical application is also used for periodontal diseases (Br. Dental J., 1977,142,366-369). Chlorhexidine gluconate 1% dental gel and 0.2% mouth wash is employed for the prevention of plaque and the prevention and treatment of gingivitis and in the treatment of oral candidiasis.

Lidocaine is a local anesthetic of amide type and is widely used in injection and for local application to mucus membranes. It has rapid onset of action and has an intermediate duration of action.

Benzocaine is ethyl ester of p-aminobenzoic acid, it is usually used to relieve pain associated with ulcers, wounds and mucous membrane. Normally it acts only as long as it is in contact with skin or mucosal surface. Peak effect occurs within 1 minute and lasts for 36 to 60 minutes.

Taking into consideration the synergestic action of all three active agents for the treatment of periodontitis and related dental problems, the inventors have described, a pharmaceutical dental gel preparation in US 6,365,131 which comprises of metronidazole benzoate, chlorhexidine gluconate, and local anesthetic as the active ingredient; glycol as the solvent medium; a carboxyvinyl polymer, cross-linked polymer of acrylic acid copolymerized with polyalkylsucrose as a gelling agent.

U.S. Pat. No. 4,764,377 issued to Goodson teaches an interpocket drug delivery device
that uses a polymeric matrix, such as ethylene vinyl acetate co-polymer, as a packing containing a therapeutic agent. The therapeutic agent diffuses out of the polymeric packing providing continuous therapy for the treatment site. This packing is not placed in the periodontal pocket in a solution or paste form.

U.S. Pat. No.4,685,883 and U.S. Pat. No. 5,059,123 teaches the use of microparticles containing chemotherapeutic agents, and their use as periodontal barriers and in methods for aiding periodontal tissue regeneration. In patent 4,685,883 the microcapsules are deposited in the periodontal pocket or attached to a root surface of the tooth for treatment of the periodontal disease. The patent 5,059,123 describes periodontal barriers made of body compatible materials (said to include resorbable and nonresorbable materials and which may also preferably incorporate microencapsulated chemotherapeutic agents) to aid periodontal tissue regeneration, where barriers are taught to be surgically implanted by conventional techniques and sutured in place by use of body compatible sutures. Both the systems are complicated and need expert assistance.

US patent No. 5,230,895 by Czarnecki, et al. described an in vivo method is described for treating a subject for periodontal disease by placing a mixture of a glyceride composition and a therapeutic agent in the periodontal pocket of subject such that the therapeutic agent is released in a sustained manner. The glyceride composition is selected such that the mixture of the glyceride composition and the therapeutic agent is capable of forming a gel in the environment of the periodontal pocket.

Dammani et al described methods for aiding periodontal tissue regeneration with compositions containing bioresorbable polymers, leachable solvents, and drug actives in US patent 5,447,725. The compositions become harder upon contact with the periodontal tissue such that the composition is effective for aiding tissue regeneration and by releasing a therapeutically effective amount of drug active agent.
In spite of such research, there continues to be a need for improved compositions and methods for aiding periodontal treatment. This application is a continuation of U.S. Pat. No. 6,365,131, which is filed Apr. 2, 2002. It would be highly desired to have bucco-adhesive dosage forms, which is retained in periodontal pockets and facilitates the release of the combination of pharmaceuticals. Of special importance would be such a mucoadhesive dosage form, which treats local infective conditions in the oral cavity.

The inventors of the present invention have come out with simple and inexpensive way of delivering actives for longer duration of action at affected site with the use of mucoadhesive agent.

RELATED APPLICATION

This application is a continuation of U.S. Pat. No. 6,365,131, which is filed Apr. 2, 2002.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the pharmaceutical mucoadhesive dental gel formulation and manufacturing process thereof for topical application in the form of aqueous gel suitable for the treatment of periodontal diseases. The present formulation comprises of Metronidazole benzoate, chlorhexidine gluconate (20% solution), the local anesthetics that are incorporated in the mucoadhesive dental gel formulations of the present invention in an amount of about 0.5 to 3.0% and 0.2 to 2 percent by the weight respectively, preferably from about 1% of active metronidazole and 0.25% active chlorhexidine by weight respectively.
The concentration of local anesthetic, especially lidocaine may range between 0.5 & 2 weight % in terms of lidocaine hydrochloride. The addition of a local anesthetic is desired also for medical reasons, for the prevention of dental pain. Preferred concentration is 0.5%.

Just like the lidocaine most of the local anesthetics are slightly basic substances forming salts with acids such as hydrochloride. The local anesthetics are expediently used in the form of their hydrochloride salt. Local anesthetics of the kind of lidocaine are, in particular, etidocaine, benzocaine. The concentration of benzocaine as a local anesthetic may vary in the range of 1 to 20% and preferred concentration is 7.5%.

As mentioned above, the mucosal adhesive dental gel of this invention contains a mucoadhesive polymer selected from starch, modified celluloses, crystalline cellulose, microcrystalline cellulose, carboxymethyl cellulose, acrylic acid copolymer, copolymer of methyl vinyl ether and maleic anhydride, polyglycolic acid, polycarbophil A. The most preferred being copolymer of methyl vinyl ether and maleic anhydride, Gantrez S 97®. The said polymer is present in the range of 2.0-20% by weight based on the total weight of the composition, preferably about 5-10% and most preferred concentration being 7.5% by weight based on the total weight of the composition.

Mucoadhesivity of the composition as described in the present invention can be attributed to interaction of gel layer of Gantrez S 97® and mucin on the contact surface. Gantrez S 97® co-polymers are water soluble giving clear, tacky solutions with a solution rheology that can be modified by the addition of salts and bases. The dosage form as described in the present invention when applied to periodontal pockets, comes in contact with gingival cravicular fluid or saliva, the mucoadhesive polymer swells, giving rise to manyfold increase in volume which facilitates maximum contact with mucin, the glycoprotein predominant in mucous layer, thus, increasing the
contact time at the desired site and releasing the drugs slowly for longer duration. Adhesion to mucosal surface improves bioavailability and thus makes the product more efficacious.

The medium for the active ingredient comprises a mixture of water and propylene glycol. Propylene glycol concentration fluctuates between 5 to 80%. Preferred concentration is 5% by weight based on the total weight of the said composition. Other medium can be used in this specification refers to Glycerin, Polyethylene glycols, but preferred is propylene glycol.

The carboxyvinyl polymer used, as the gelling agent in the present invention is a hydrophilic polymer obtained by the polymerization of acrylic acid as the principal component. Preferred molecular weight of the polymer is in the range of $4 \times 10^6$. Polymer present in the composition is in the range of 0.2 to 7% by weight based on the total weight of the said composition. Preferred polymer is carbomer 940 in said gelling agent in the present invention is selected from carbomer 940, carbomer 934, Hydroxypropylmethylcellulose, sodium carboxymethylcellulose.

If the pH of the gel formulation of the present invention is on considerably acidic or basic side then it is desirable to add the pH modifier to the preparation of the present invention to adjust its pH in the range of 4.5 – 7, preferably 5 to 6. There are no specific limitations as to the kind of the pH modifiers are inorganic pH modifier, e.g. sodium hydroxide or potassium hydroxide. Preferred pH modifier in the resent invention is sodium hydroxide solution.

An auxiliary agents used in the present invention are comprised of disodium EDTA menthol, and sodium saccharin, were added to the gel preparation of this invention.
Menthol imparts the cooling effect, EDTA acts as chelating agent and antioxidant, and sodium saccharin gives the sweetness to the dental gel. It is suitably incorporated in an amount of from about 0.025 to 0.5 percent by weight of the preparations.

Chelating agent used in this specification refers to disodium EDTA, Edetic acid, citric acid, Disodium calcium EDTA. Flavouring agent which imparts soothing action refers to menthol, peppermint oil, spearmint oil, clove oil. Sweetening agent here refers to Saccharin sodium, aspartame, Dihydrochalcones, D-tryptophan etc.

The present invention will now be further illustrated by, but is by no means limited to, the following examples wherein preferred embodiments of the metronidazole benzoate and chlorhexidine gluconate and local anesthetic containing dental gel preparations are expressed on the weight basis. Those who are skilled at the art can decide the percentage of other/auxiliary agents used to formulate the different example described below.

The following examples are provided to illustrate the present invention and should not be misunderstood to limit the scope of the present invention in any way.

EXAMPLES

Example 1

<p>| Metronidazole (as Metronidazole benzoate) | 1.0% |
| Chlorhexidine gluconate (20% solution) | 0.25% |
| Lidocaine hydrochloride | 0.5% |
| Propylene glycol | 5.0% |
| Carbomer 940® | 1.5% |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Gantrez S 97°</td>
<td>7.5%</td>
</tr>
<tr>
<td>Disodium EDTA</td>
<td>0.025%</td>
</tr>
<tr>
<td>Sodium saccharine</td>
<td>0.1%</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.5%</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>PH modifier</td>
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</tbody>
</table>

Preparation Method:

The gel preparations of the invention can be prepared for example, by initially dissolving menthol in propylene glycol to this solution active metronidazole is added in portion with continuous stirring. Add carboxyvinyl polymer (carbomer 940) and copolymer of methyl vinyl ether and maleic anhydride (Gantrez S 97) in portion with continuous stirring with homogenizer to form gel at 30 to 35°C. To the gel thus obtained is added a separately prepared aqueous solution of disodium EDTA, sodium saccharin, lidocaine hydrochloride and chlorhexidine gluconate with stirring till it dissolve. Further, sodium hydroxide, pH modifier is added to the resulting gel preparation, with stirring, in an amount sufficient to adjust the pH of the resulting gel preparation to about 5 to 6 which will form uniform viscous gel.

Example 2

<p>| Metronidazole(as Metronidazole benzoate) | 1.0% |
| Chlorhexidine gluconate(20% solution) | 0.25% |
| Benzocaine hydrochloride | 7.5% |
| Propylene glycol | 5.0% |
| Carbomer 940° | 1.5% |
| Gantrez S 97° | 7.5% |</p>
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disodium EDTA</td>
<td>0.025%</td>
</tr>
<tr>
<td>Sodium saccharine</td>
<td>0.1%</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.5%</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>PH modifier</td>
</tr>
</tbody>
</table>

A one-kg batch of composition of the present invention prepared as follows:
To 850 purified water, 0.25 gm disodium EDTA, 1 gm of sodium saccharin, and 2.5 gm of chlorhexidine gluconate solution B.P. were added dissolved with stirring. On other hand 5gm of menthol was separately dissolved in 50gm of propylene glycol, to this 16 gm of metronidazole benzoate and 75 gm of benzocaine was then added and dispersed with continuos stirring, further 15gm of carbomer 940 and 75gm of Gantrez S 97® were added to mixture with continuos stirring with homogenizer. To the gel thus obtained, added aqueous solution prepared above of disodium EDTA, sodium saccharin, and chlorhexidine gluconate with stirring till it dissolve. The pH of gel was then adjusted between 5 to 6 with 10% sodium hydroxide solution. The final weight of the gel was adjusted to one Kg addition of distilled water and mixed well.

**CLINICAL TRIALS**

To investigate the effectiveness of the present invention in periodontitis and other related diseases like dry sockets and apthous ulcer stomatitis, multicentric controlled clinical trials were carried out at five different centers all over India. Number of patients of different age groups were included in the trial.

These study is not disclosed to the public and the trials were done in confidence. The results of clinical study in India is given below.
1. Randomised and double blind study to evaluate the efficacy and safety of mucoadhesive combination of Metronidazole Benzoate, chlorhexidine and Benzocaine in patients of gingivitis and periodontitis in comparison to non mucoadhesive combination.

This study was carried out to evaluate the efficacy and safety of combination of Metronidazole Benzoate, chlorhexidine gluconate and Benzocaine formulated in mucoadhesive gel in patients of gingivitis and periodontitis. 70 patients of either sex diagnosed to having gingivitis/ periodontitis were enrolled in the trial after taking the ethics committee permission. Patients were divided into two groups, Group one received the combination with property of mucoadhesion and group II received the combination without mucoadhesive for a period of 4 weeks. The patients were included in the study if they had at least 1 tooth in each quadrant with a probing pocket depth (PPD) of 5 mm or more in at least 1 of the 4 sites; mid- mesial, mid distal, mid lingual or mid buccal aspect. 778 sites were treated and measured for PPD on week 8 after drug treatment. From group I, out of 35, 33 had improved 1 mm or more and 2 improved to about 1mm. In group B, 22 had improved 1 mm or more and 13 improved to about 1 mm. The bleeding on probing was similar in both groups. Before treatment the overall mean BOP was 85%. The overall mean reductions were 68 percentage points after application of the combination gel with mucoadhesive properties (group I) and 52 percentage points after application of the combination gel without adhesive properties (group II). No adverse experiences were reported in either group. The statistical significance found in the first group can be attributed to the mucoadhesiveness of the combination of metronidazole benzoate, chlorhexidine and benzocaine.

2. Randomised and double blind study to evaluate the efficacy and safety of mucoadhesive combination of Metronidazole Benzoate, chlorhexidine and
Benzocaine in patients of gingivitis and periodontitis in comparison to non-mucoadhesive combination.

In another study which evaluated the efficacy and safety of combination of Metronidazole Benzoate, chlorhexidine gluconate and Benzocaine from mucoadhesive dental gel formulation used for the treatment of patients suffering from gingivitis and periodontitis. 50 patients of either sex diagnosed to having gingivitis/periodontitis were enrolled in the trial after taking the ethics committee permission. Patients were divided into two groups, group A received the combination comprising mucoadhesive agent and group B received the combination without mucoadhesion for a period of 4 weeks. The patients were included in the study if they had at least 1 tooth in each quadrant with a probing pocket depth (PPD) of 5 mm or more in at least 1 of the 4 sites; mid-mesial, mid distal, mid lingual or mid buccal aspect. 568 sites were treated and measured for PPD on week 8 after drug treatment. In group A out of 25, 21 had improved 1 mm or more and 4 improved to about 1 mm. In group B, 17 had improved 1 mm or more and 7 improved to about 1 mm. The bleeding on probing was similar in both groups. Before treatment the overall mean BOP was 78%. The overall mean reductions were 54 percentage points after application of the combination gel with mucoadhesive properties (group A) and 37 percentage points after application of the combination gel without adhesive properties (group B). No adverse experiences were reported in either group. The statistical significance found in the group A was found due to the mucoadhesiveness of the combination of metronidazole benzoate, chlorhexidine gluconate and benzocaine.

Above clinical trials confirms the efficacy of the mucoadhesive dental gel formulation of this invention in following conditions like--

a. Chronic gingivitis (Edematous, Hyperplastic and Atrophic)
b. Acute ulcerative gingivitis
c. Chronic periodontitis
d. To prevent post extraction infections (dry socket)
e. In recurrent apthous stomatitis (Ulcer)
f. Dental pain due to infections.

It is to be understood that the example and embodiments described hereinabove are for the purpose of providing a description of the present invention by way of example and are not to be viewed as limiting the present invention in any way. Various modifications or changes that may be made to that described hereinabove by those of ordinary skill in the art are also contemplated by the present invention and are to be included within the spirit and purview of this application and the following claims.
We Claim

1. A novel pharmaceutical dental gel formulation for topical application in the form of mucoadhesive aqueous gel comprising a therapeutically effective amount of metronidazole benzoate, chlorhexidine gluconate, and a local anesthetic gelled with a hydrophilic polymer, an aqueous medium, a chelating agent, a sweetening agent, a mucoadhesive agent, a flavoring agent, and a pH modifier, suitable for the treatment of periodontal diseases which mainly include gingivitis, stomatitis, aphthous ulcer, post extraction infection.

2. A novel pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein the concentration of said metronidazole benzoate and Chlorhexidine gluconate is in the range of 1 to 2% and 0.2 to 2% weight based on the total weight respectively of said composition.

3. A pharmaceutical mucoadhesive dental formulation in accordance with claim 2, wherein the preferred concentration of metronidazole benzoate is 1%, chlorhexidine gluconate is 0.25% weight based on the total weight of the said composition.

4. A pharmaceutical mucoadhesive dental formulation in accordance with claim 2, wherein the concentration of metronidazole benzoate is at least about 0.8%, chlorhexidine gluconate is at least about 0.01% weight based on the total weight of the said composition.

5. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein the used local anesthetic used is either lidocaine hydrochloride or benzocaine.
6. A pharmaceutical mucoadhesive dental formulation in accordance with claim 5, where in concentration of lidocaine hydrochloride and benzocaine is in the range of 0.5 to 2% weight based on the total weight of said composition respectively.

7. A pharmaceutical mucoadhesive dental formulation in accordance with claim 6, the preferred concentration of lidocaine hydrochloride and Benzocaine is 0.5% and 7.5% weight based on the total weight of said composition respectively.

8. A pharmaceutical mucoadhesive formulation in accordance with claim 6, wherein the concentration of lidocaine hydrochloride is at least about 0.5% and benzocaine is at least about 1% weight based on the total weight of said composition.

9. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein a mucoadhesive polymer is selected from starch, modified celluloses, crystalline cellulose, microcrystalline cellulose, carboxymethyl cellulose, acrylic acid copolymer, copolymer of methyl vinyl ether and maleic anhydride, polyglycolic acid, polycarbophil A. The most preferred being copolymer of methyl vinyl ether and maleic anhydride, Gantrez S 97®. The said polymer is present in the range of 2.0-20% by weight based on the total weight of the composition, preferably about 5-10% and most preferred concentration being 7.5% by weight based on the total weight of the composition.

10. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, containing gelling agent is hydrophilic and water dispersible polymer present can be chosen from carbomer 940, carbomer 934, hydroxypropyl...
methlcellulose, sodium carboxymethylcellulose in the range of 0.2 to 7% by weight based on the total weight of said composition.

11. A pharmaceutical mucoadhesive dental formulation in accordance with claim 10, wherein said gelling agent should be preferably carbomer 940 in an amount about 1.5% weight based on the total weight of the said composition.

12. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein said medium used is water and glycol.

13. A pharmaceutical mucoadhesive dental formulation in accordance with claim 12, wherein said glycol is selected from propylene glycol, glycerin, polyethylene glycols.

14. A pharmaceutical mucoadhesive dental formulation in accordance with claim 13, wherein said glycol is preferably propylene glycol present in a range of about 2% to about 10% preferably 5% by weight based on the total weight of said composition.

15. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein said chelating agent is chosen from Disodium EDTA, Edetic acid, Citric acid, Disodium calcium EDTA.

16. A pharmaceutical mucoadhesive dental formulation in accordance with claim 15, wherein said chelating agent is Disodium EDTA, in the range of about 0.01% to about 0.01% to about 0.1% preferably 0.025% by weight based on the total weight of said composition.
17. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein said sweetening agent is selected from the group consisting of saccharine sodium, aspartame, dihydrochalcones, tryptophan etc.

18. A pharmaceutical mucoadhesive dental formulation in accordance with claim 17 wherein said sweetening agent preferably is saccharin sodium.

19. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, wherein the said flavoring agent can be menthol, peppermint oil, spearmint oil, anise oil, and clove oil.

20. A pharmaceutical mucoadhesive dental formulation in accordance with claim 19, wherein said flavoring agent preferably is menthol.

21. A pharmaceutical mucoadhesive dental formulation in accordance with claim 1, having pH in the range of 4.5 to 7, preferably having pH 5 to 6.

22. A pharmaceutical mucoadhesive dental formulation used for periodontal diseases substantially as herein described in the examples herein described.
# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER

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<tr>
<th>IPC(7)</th>
<th>A 61K 7/16; A 61K 31/353; A 61K 9/70; A 61K 9/06; A 61L 15/44</th>
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<td>US CL</td>
<td>424/49; 424/445; 424/447; 424/449; 514/817; 514/944; 514/969</td>
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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)

U.S.: 424/49; 424/445; 424/447; 424/449; 514/817; 514/944; 514/969

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 practicable, search terms used)

WEST 2

## 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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<tr>
<td>X</td>
<td>U.S. 6,365,131 B1 (M. DOSHI et al.) 02 APRIL 2002 (See the entire document, Examples 1 and 2 therein correspond to examples 1 to 6 therein; claims 1 to 21 therein):</td>
<td>1 to 21</td>
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<td>Y</td>
<td>U.S. 6,017,516 (S. MDDY et al.) 25 JANUARY 2000 (See the entire document, the same aqueous dental gel of metronidazole benzole and chlorhexidine gluconate, but without any local anesthetic component;</td>
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<td>A</td>
<td>U.S. 5,446,063 (G. REUTER et al.) 29 AUGUST 1995 (see Example 8, claim 4, columns 5 and 6, an aqueous benzocaine anesthetic topical gel).</td>
<td>1 to 21</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

| Special categories of cited documents: | | |
|--------------------------------------|----------------------|
| "A" document defining the general state of the art which is not considered to be of particular relevance | "+" laser 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 |
| "E" earlier application or patent published on or after the international filing date | "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 |
| "L" document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified) | "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 |
| "O" document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

17 March 2003 (17.03.2003)

Date of mailing of the international search report

08 AUG 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

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Washington, D.C. 20231

Authorized officer

Marianne Seidel

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)