Sustained Release of Topical Anesthetics

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A composition and method to alleviate oral mucosal discomfort and irritation in an orthodontic patient. A wax matrix containing less than 15% analgesic/anesthetic agent such as benzocaine and excipients enhanced and extended release of the analgesic/anesthetic agent compared to known art formulations. The composition exhibited desirable aesthetic properties, was easy to apply, and the relatively lower concentration of active agent provided enhanced safety.

22 Claims, 2 Drawing Sheets
References Cited

OTHER PUBLICATIONS

**Fig. 1**

A graph showing the relationship between **Avg Absorbance at 284 nm** and **Avg Conc of Benzocaine in uM**. The equation of the line is given as:

\[ y = 0.0192x - 0.0089 \]

with a correlation coefficient of **R^2 = 0.9985**.

**Fig. 2**

A graph showing the relationship between **Avg % Drug Released** and **Time in min**. The equation of the line is given as:

\[ y = 0.101x + 3.726 \]

with a correlation coefficient of **R^2 = 0.9717**.
1
SUSTAINED RELEASE OF TOPICAL ANESTHETICS

This application claims priority to co-pending U.S. application Ser. No. 61/721,567 filed Nov. 2, 2012 which is expressly incorporated by reference herein in its entirety.

The discomfort and irritation of the oral mucosa that an orthodontic patient experiences during treatment is caused by friction between the oral mucosa and the orthodontic brackets. Administering painkillers or applying a commercially available non-medicated orthodontic wax over the brackets are options for orthodontic patients. However, orthodontic wax simply prevents friction and avoids further irritation, but does not reduce discomfort.

Commercially available non-medicated waxes for use in orthodontics include, e.g., GUM® Orthodontic Wax. Commercially available medicated products contain, for the most part, 20% benzocaine. “Dent’s Extra Strength Toothache Gum” (Grandpa Brands, Erlanger, KY) is advertised as a medicated wax to place in an exposed tooth cavity or as a protective cover for a chipped tooth. It contains benzocaine 20%, beeswax, petrolatum, cotton, flavor, FD&C Red No. 40 AI. Lk. However, hypersensitivity reactions to beeswax have been reported, and beeswax and petrolatum are insoluble in water. There was a voluntary product recall (May 2012) due to excessive benzocaine levels in some lots.

The disclosed method and composition is an orthodontic wax matrix that provides sustained release of an analgesic/anesthetic agent, also termed “active”, that is used in to alleviate oral mucosal discomfort, with the analgesic/anesthetic agent present in the matrix at a concentration that is relatively lower compared to known formulations. In one embodiment, the analgesic/anesthetic agent is benzocaine, which is the ethyl ester of para-aminobenzoic acid (PABA). In one embodiment, benzocaine is present in the matrix at a concentration from 0.1% up to less than 15%. In one embodiment, the disclosed method and composition is an orthodontic wax that contains an analgesic/anesthetic agent at a concentration lower than that previously used, and at least one excipient that provides sustained release of the analgesic/anesthetic agent from the wax matrix over at least eight hours. The composition is applied to an orthodontic bracket or brace of an orthodontic patient to relieve discomfort up to 24 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a calibration curve for the optical measurement of varying concentrations of benzocaine in an artificial saliva simulator by absorbance spectroscopy at 284 nm. FIG. 2 illustrates the time release of benzocaine from an exemplary composition into an artificial saliva simulant, as determined by measurements using absorbance spectroscopy at 284 nm.

FIG. 3 illustrates an exemplary composition applied to an orthodontic bracket or brace affixed to a tooth of a patient.

DETAILED DESCRIPTION

As used herein, all percentage concentrations are weight/weight. As used herein, all concentration ranges are inclusive in that the upper and lower values are included within the range, and in that all sub-ranges within the range are encompassed. For example, and by way of illustration only, a range of 0%-10% concentration of a component includes the absence of that component (0%), and every concentration up to and including 10% (e.g., 0.01%-10%, 0.1%-10%, 0.2%-10%, 0.1%-9.9%, 0.1%-8.9%, and so on).

In one embodiment, the formulation contains xanthan gum as a sustained release agent, and benzocaine (each from Spectrum) as the analgesic/anesthetic agent. In one embodiment, this formulation additionally contains microcrystalline wax (Koster Keunen), glyceryl monostearate, heavy mineral oil, PEG 1500, and Tween 80.

Tables 1A and 1B show exemplary formulations.

| TABLE 1A |
| Ingredients | Weight in g | % | Microcrystalline wax | 21 | 83 |
| Glyceryl monostearate | 0.67 | 2.7 |
| Heavy mineral oil | 0.25 | 1.0 |
| PEG 1500 | 1.25 | 5.0 |
| Benzocaine | 1.25 | 5.0 |
| Tween 80 | 0.083 | 0.3 |
| Xanthan gum | 0.75 | 3.0 |

| TABLE 1B |
| Ingredients | Weight in g | % used in artificial saliva in vivo release evaluation | Microcrystalline wax | 21 | 83 | 50-99 |
| Glyceryl monostearate | 0.67 | 2.7 | 0-10 |
| Heavy mineral oil | 0.25 | 1.0 | 0-30 |
| PEG 1500 | 1.25 | 5.0 | 0-30 |
| Anesthetic/analgistic | 1.25 | 5.0 | 0.01-14.9 |
| Tween 80 | 0.083 | 0.3 | 0-10 |
| (Polysorbate 80) Xanthan gum | 0.75 | 3.0 | 0-30 |

As shown above, in embodiments, excipients are added to improve product characteristics. In general, in the above formulation of analgesic/analgistic agent, the microcrystalline wax provides a matrix; glyceryl monostearate has known properties as an emollient, solubilizing agent, stabilizing and sustained-release ingredient; heavy mineral oil has known properties as an emollient, lubricant, and oleaginous vehicle making the wax softer and less rigid; polyethylene glycol-1500 (PEG 1500) enhances matrix hydrophilicity; Tween 80 (Polysorbate 80) serves as a wetting/dispersing/suspending agent in lipophilic bases; and xanthan gum is a stabilizing agent and suspending agent, as described in the Handbook of Pharmaceutical Excipients (7th Edition, London: Pharmaceutical Press, 2012), the relevant sections of which are expressly incorporated by reference herein in their entirety.

The following instruments were used in evaluations: Mettler AE 200 weighing balance, 4802 UV/Vis double beam spectrophotometer, and Hanson Vision Elite 8 dissolution apparatus.

Microcrystalline wax was melted in a beaker placed in a water bath maintained at 90° C. Once melted, glyceryl monostearate was added, followed by 250 μL heavy mineral oil with mechanical stirring. At about the same time, PEG 1500 was melted in another beaker placed in a water bath maintained at 90° C. and stirred using a magnetic stirrer at 80 rpm. Benzocaine was added in portions every 2.5 min over a period of 12.5 min waiting for each addition to solubilize before adding the next. Tween 80 was added with continuous stirring and heat. Xanthan gum was then added in 0.25 g quantities over a period of two min while increasing stirring to 150 rpm. The wax mixture was poured into the PEG-drug mixture over two to three min while stirring at 200 rpm and stirred for an additional five min. The two mixtures were stirred mechanically with visual inspection. As soon as the wax began to solidify, the mixture was poured into a mold.

The formulation of Table 1A was assessed for an in vitro benzocaine release profile from the wax using an artificial saliva formulation that was prepared according to Table 2.
The in vitro benzocaine release study used the artificial saliva formulation containing potassium phosphate monobasic (K\(_2\)HPO\(_4\)), sodium phosphate dibasic (Na\(_2\)HPO\(_4\)), potassium carbonate (K\(_2\)CO\(_3\)), sodium chloride (NaCl), magnesium chloride hexahydrate (MgCl\(_2\)·6H\(_2\)O), calcium chloride (CaCl\(_2\)), citric acid anhydrous, dilute hydrochloric acid (HCl), methanol, and MilliQ filtered water (resistivity=18.0 megohms). Each ingredient was dissolved in 150-200 mL MilliQ filtered water and poured in a 4 L volumetric flask placed on a stirrer (350 RPM). K\(_2\)HPO\(_4\), Na\(_2\)HPO\(_4\), and MgCl\(_2\) were ground before weighing. The final pH of the solution was adjusted to 6.7 using dilute HCl.

A standard curve of benzocaine was prepared. One mg benzocaine was dissolved in 20 mL methanol to make a stock solution. The stock solution was used to make 5 mL of increasing concentrations of benzocaine in artificial saliva (5 \(\mu\)M, 10 \(\mu\)M, 2.5 \(\mu\)M, 25 \(\mu\)M, 30 \(\mu\)M, 45 \(\mu\)M, 50 \(\mu\)M, 55 \(\mu\)M, and 60 \(\mu\)M). Absorbance of each concentration was measured at 284 nm using a UV/Vis double beam spectrophotometer. The cuvette was washed 3-4 times with water between each measurement. Each measurement was performed in triplicate, with the average absorbance of each concentration used to generate the standard curve.

A Hanson Vision Elite 8 dissolution apparatus was used for the in vitro benzocaine release study. Degassed artificial saliva was the dissolution medium (900 mL.). The paddle speed was 50 rpm and the water bath was maintained at 37°C. Five mL of medium was withdrawn at each time point (0 min, 30 min, 60 min, 120 min, 180 min, 240 min, 300 min, 360 min, 420 min, 480 min, and 77 hours) and replaced by an equal volume of warm artificial saliva. Sinkers were used to place about 150 mg benzocaine wax in each basket.

The results of a standard benzocaine curve prepared in artificial saliva are reported in Table 3 and shown in FIG. 1.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artificial saliva formulation</td>
</tr>
<tr>
<td>Components</td>
</tr>
<tr>
<td>K(_2)HPO(_4)</td>
</tr>
<tr>
<td>NaCl</td>
</tr>
<tr>
<td>MgCl(_2)</td>
</tr>
</tbody>
</table>

pH adjusted to 6.7 with dilute HCl

The results of in vitro release of 5% benzocaine, formulated as shown in Table 1A, in the artificial saliva formulation from Table 2 are reported in Table 4 and shown in FIG. 2.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time release profile of benzocaine into artificial saliva formulation</td>
</tr>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>120</td>
</tr>
<tr>
<td>180</td>
</tr>
<tr>
<td>240</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>360</td>
</tr>
<tr>
<td>420</td>
</tr>
<tr>
<td>480</td>
</tr>
</tbody>
</table>

As the data show, this formulation had an average of 56% percent benzocaine released into the artificial saliva medium after eight hours. This release rate was more than twice that obtained for a previous first-generation formulation described in U.S. Pat. No. 6,874,674 (the '674 patent) which is expressly incorporated by reference herein in its entirety. The '674 patent formulation was 7.1% tragacanth, 70.9% microcrystalline wax, 2.0% Span 80, and 20.0% benzocaine. The '674 patent formulation had an in vitro release of only 22.7% benzocaine released into the medium after eight hours. This difference was unexpected. Without being limited to a specific theory, and with all other variables being equal, Fick’s Law of Diffusion would predict a greater release of analgesic/anesthetic agent from a matrix that contains a higher concentration of the analgesic/anesthetic agent. From the results shown herein, however, a greater percent of benzocaine was released from the disclosed formulation that contained a relatively lower benzocaine concentration, compared to that in the '674 patent. Specifically, the analgesic/ anesthetic agent that was released from the formulation now disclosed was 11.3% at 1 hr, 16.6% at 2 hr, 18.8% at 3 hr, 23.8% at 4 hr, 29.7% at 5 hr, 39.8% at 6 hr, 48.3% at 7 hr, and 56.0% at 8 hr. The analgesic/anesthetic is released in one embodiment up to 24 hr.

In embodiments using a sustained release agent, xanthum gum provided both a good release rate and a good product aesthetic appearance. Without being bound by a specific theory, this may be due to the structure of the xanthum gum
The ingredient may be used in embodiments of the formulation as follows:

**Analgésic/anesthetic agents, also termed active agents:**
These include benzocaine, lidocaine, novocaine, procaine, buta- laine, dyclonine, prilocaine, tetracaine, butamben (butyl benzyl alcohol), and combinations thereof. The formulations disclosed herein have a lower concentration of analgesic/anesthetic agent. This results in enhanced patient safety and ease of regulatory approval, while also providing an enhanced release profile for increased efficacy. The formulations disclosed herein have an improved aesthetic appearance, facilitating patient use and compliance, and are more similar to unmedicated waxes, and less similar to the tragacanth-containing wax described in the '674 patent with a yellow appearance. The increased percentage of the wax matrix assists in retaining a wax-like character; sufficiently flexible to be broken off of a wax strip and applied to an orthodontic bracket without crumbling or falling apart, as shown in FIG. 3. This increases both patient acceptability, as well as formulation retention on orthodontic brackets. In use, the wax is applied to the bracket. It will then be in contact with the mucosa as the gums lay against the teeth. Without the wax, the mucosa lays against the metal bracket; this is the source of irritation to the mucosa. The wax will stay on the metal bracket because the wax is malleable. The wax will be molded onto the part of the bracket that protrudes and is in contact with the mucosa.

Several excipients are used in the formulations to provide for improved patient acceptability, as well as other properties. These excipients may be included to optimize or otherwise improve the formulation. For example, in one embodiment, the surfactant is polysorbate 20. In another embodiment, the surfactant is polysorbate 80. In other embodiments, the surfactant is comprised of a mixture of polysorbate 20 and 80. In a further embodiment, the surfactant is comprised of a mixture of polysorbate 20, 80 and 60.

The excipients may also be utilized to provide additional functionality to the formulations. For example, in one embodiment, the excipient is a mixture of hydrated sodium alginate and carrageenan gum. In another embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin A. In a third embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin B. In a fourth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin C. In a fifth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin D. In a sixth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin E. In a seventh embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin F. In an eighth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin G. In a ninth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin H. In a tenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin I. In an eleventh embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin J. In a twelfth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin K. In a thirteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin L. In a fourteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin M. In a fifteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin N. In a sixteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin O. In a seventeenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin P. In an eighteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin Q. In a nineteenth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin R. In a twentieth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin S. In a twenty-first embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin T. In a twenty-second embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin U. In a twenty-third embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin V. In a twenty-fourth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin W. In a twenty-fifth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin X. In a twenty-sixth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin Y. In a twenty-seventh embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin Z. In a twenty-eighth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin AA. In a twenty-ninth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin BB. In a thirtieth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin CC. In a thirty-first embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin DD. In a thirty-second embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin EE. In a thirty-third embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin FF. In a thirty-fourth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin GG. In a thirty-fifth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin HH. In a thirty-sixth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin II. In a thirty-seventh embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin JJ. In a thirty-eighth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin KK. In a thirty-ninth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin LL. In a forty-first embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin MM. In a forty-second embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin NN. In a forty-third embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin OO. In a forty-fourth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin PP. In a forty-fifth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin QQ. In a forty-sixth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin RR. In a forty-seventh embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin SS. In a forty-eighth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin TT. In a forty-ninth embodiment, the excipient is a mixture of hydrated sodium alginate and cecropin UU.
droxyethyl cellulose ether, hydroxyethyl ether cellulose, hydroxyethyl starch, hyetellose, NATROSOL™, oxycellu-
lose, Tylose PHA); hypromellose (also known as BENECEL®, HPMC, E464, hydroxypropyl methylcellulose,
HPMC, METHOCEL®, methylethylcellulose propylene glycol ether, methyl hydroxypropylcellulose, METHOCEL®,
TYLOPUR™); hypromellose acetate succinate (also known as AQQAT®, AQQAT® AS-HE/HG, AQQAT® AS-LF/LG,
AQQAT® AS-MF/MG, cellulose 2-hydroxypropyl methyl ether acetate succinate, HPMCAS); hypromellose phthalate
(also known as cellulose phthalate hydroxypropyl methyl ether, HPMC, hydroxypropyl methylcellulose benzene-1,2-
dicarboxylate, 2-hydroxypropyl methylcellulose phthalate, methylhydroxypropylcellulose phthalate); kaolin (also
known as Argilla, bulus alba, China clay, E559, kaolinite, Lion, porcelin clay, Sim 90, weisserton, white bole); mag-
nesium aluminum silicate (also known as aluminoisic acid magnesium salt, aluminum magnesium silicate, Carrisbor-
GELSORB™ MAGNABRUTE®, magnesium aluminosilicate, magnesium aluminum silicate colloidal, magnesium
aluminum silicate complex colloidal, NEUSILIN®, Pharm-
sorb, silicic acid aluminum magnesium salt, Veegum); meth-
ylethylcellulose (also known as BENECEL®, CULINAL®
MC, E461, METHOCEL®, METOLOSE®); polacrilin
potassium (also known as AMBERLITE® IRA-88, salt, polyacrylic acid polymer with divinylbenzene potassium salt,
polacrilin kalii); polycarbophil (also known as NOVEON®
AA-1); polyethylene oxide (also known as POLYX®, polyoxirane, polyoxyethylene); polyethy-
lacrates (also known as ACRYL-EZE®, ACRYL-EZE® MP,
EASTACRYL® 30D, EUDRAGIT®, KOLLIQOAT® MAE
30 D, KOLLIQOAT® MAE 30 DP; polymeric methacrylates;
USP/NF non-proprietary names are Ammonia methacrylate copolymer, methacrylic acid copolymer, methacryl-
ic acid copolymer dispersion; saponite (also known as Alford, alu-
imino-p-saponite, axtite, catkinite, ferroan saponite, grif-
fithite, licanite, lucianite); sodium starch glycolate (also
known as carboxymethyl starch sodium salt, EXPOLOS®,
EXPLOTA®, GLYCOLYS®, PRIMOJEL®, starch
boroxymethyl ether sodium salt, TABLOTM, VIVASTAR® P); starch (also known as Amido, amidon, amylum, amy-
lyt, P™ PHARMGEL®, FLUFTEX™ W, INSTANT
PURE-COTE®, MELOJEL®, Meriten, PAYGEL® 55,
PERFECTAMYL® D6PH, PURE-BIND®, PURE-COTE®,
PURE-DENT®, PURE-GEL®, PURE-SET®, Purity 21,
Purity 826, Tablet White); tragacanth (also known as Alga-
roba, carob bean gum, carob flour, ceratonia gum, ceratonia
siliqua, ceratonia siliqua gum, Cheshire gum, E410, gomme
de caroube, locust bean gum, Meoprop, St. John’s brand); xanthan gum (also known as corn sugar gum, E415,
KEITROL®; polysaccharide D-1459, RODIGEL®, VAN-
ZAN® NF, XANTURAL®); D-a-tocopherol (Vitamin E)
(also known as COPHEROL® F1300, -3,4-dihydro-2,5,7,
8-tetramethyl-2-(4,8,12-trimethyldrieiclyl)-211-1-benzopy-
ran-6-ol; E307, EASTMAN® Vitamin E TPGS, synthetic
alkaline tocopherol, all-rac-atocopherol, dl-a-tocopherol, 5,7,8-
trimethyloctol); benzalkonium chloride (also known as alky-
benzyltrimethylammonium chloride, alkyl dimethyl benzyl
ammonium chloride, BKC, HYAMINE® 3500, Pentonium,
ZEPHIRAN®); cetostearyl alcohol (also known as cetacry-
alcohol, CRODACOL™ CS90, LANETTE® O, TEGO®
Alkanol 1618, Tego Alkanol 6855); cetrimide (also known as BROMAT®, Cetab, CETAVLON®, Cetrol, Lissolamine V,
Micol, Moran Chsa, Morhas, Quamous, Suricite); cetylpyridinium chloride (also known as C16-alkylpyri-
dinium chloride, CAPACOL®, Cepacol chloride, Ceratium,
cetyl pyridium chloride; Dobanen, hexadecylpyridinium
chloride, 1-hexadecylypyridinium chloride, Medilave, Prista-
cin; Pyrisset); diethanolamine (also known as bis(hydroxy-
ethyl)amine, DEA, diethylamine, 2,2-dihydroxydiethy-
lamine, diolamine, 2,2-imidodithanol); docosane sodium
(also known as bis(2-ethylhexyl) sodium sulfosuccinate, dio-
cytl sodium sulfosuccinate, DSS, sodium dioctyl sulfosucci-
nate, sulfobutanoic acid, 1,4-dio-(2-ethylhexyl) ester
sodium salt); glycercel monostearate (also known as CAP-
MUL® GMS-50, CUTINA®, GMS, 2,3-dihydroxypropyl
octodecanate, glycercine monostearate, glycercin monostear-
te, glycercel monostearate, glycercol stearate, glycercyl stea-ate, GMS, IMWITOR® 191, IMWITOR® 900, KESSCOTM
GMS, Lipo GMS 410, Lipo GMS 450, Lipo GMS 600,
monoster with 1,2,3-propanetriol, monostearin, MYVA-
PLEX™ 600P, MVAVETEXTM, 1,2,3-propanetriol
octodecanate, Protachem GMS-450, Ritu GMS, stearic acid
monoster with glycercol, stearic monoglyceride, STEPAN™
GMS, TEGIN®, TEGIN® 503, TEGIN® 515, TEGIN®
4100, TEGIN® M, UNIMATE® GMS); laureic acid (also
known as C-1297, docosanoic acid, docosic acid, duode-
ceic acid, n-dodecanic acid, HYDROFOL® acid 1225,
HYDROFOL® acid 1295, HYSTRENE® 9512, laurose-
canic acid, Neo-fat 12, Neo-fat 12-43, NINOL® AA62 Extra,
1-undecanecarboxylic acid, vulvic acid, Wecoline 1295); lecitin
(also known as E322, egg lecitin, LSC 5050, LSC 6040,
mixed soybean phosphatides, ovolecitin, PHOSAL® 53
MCT, PHOSPHOLIPON® 100 H, soybean lecitin, soybean phospholipids, Stempur, vegetable lecitin); Macrogl
15 hydroxystearate (also known as 12-hydroxystearic acid
copolymer with alpha-hydroxyhydroxypoly(oxy-1,2-
ethanediyl), polyethylene glycol 600 12-hydroxystearate,
SOLUTOL® HS 15); medium-chain triglycerides (also
known as BERGABEST®, caprylic/capric triglyceride,
CAPTIX® 300, CAPTIX® 355, CRODAMOL® GT/C,
glycerol tricaprylate/caprate, LABRAFAC™ CC; MCT oil,
MIGLYOL® 810, MIGLYOL® 812, MYRITOL®,
NEOEBE® M5, Nesatol, oleum neutral, oleum vegetable
treme, thin vegetable oil, Wagliom 3 9/280); monotheran-
olamine (also known as 1-aminoethyl alcohol, colamine, ethyl-
rolamine, 1-hexadecylglycerol, 2-hydroxylhexadecylamine; myristic acid and its salts (also known as EDENOR®
C14 98-100, n-tetradecanoic acid, 1-tridecanecarboxylic acid);
palmitic acid and its salts (also known as cetlylic acid, EDEN-
OR® C16 98-100, EMERSOL® 140, EMERSOL®
143, n-hexadecanoic acid, hexadecylic acid, HYDROFOL™,
HYSTRENE® 9016, INDUSTREN™ 4516, 1-pentadecanecar-
boxylic acid, hexadecanoic acid sodium salt, palmitec
sodium salt, sodium hexadecanoate, myricyl palmitate); Poloxamer (also known as Lutrol, MONOLAN™, PLU-
RONIC®, poloxalol, polyethylene-propylene glycol copoly-
comer, polyoxyethylene-polyoxypropylene copolymer,
Supronic, SYNERONIC®); polyoxyethylene alkyl ethers
(synonyms applicable to poloxethylene alkyl ethers are
BRIL® , CREMOPHOR® A, CYCLOGOL™ 1000,
EMPLITAN® KB, EMPLITAN® KM, EMULCENT®, ETHYLAN™ C, macrogl ethers, MARLOWET®, PLU-
RAFACTM, PROCOL®, Ritoleth, Ritox, Texofor A, Volpo);
polyoxylethylene castor oil derivatives (also known as ACCO-
NON® , ARLATONE® , CREMOPHOR®, ETOCAS™,
EUMULGIN®, JEECHEM®, LIPOCEL®, MAPEG®,
MARLOWET®, NIKOLL®, Protachem, SIMULSOL™;
polyoxylethylene sorbitan fatty acid esters (also known as
Twens, polysorbates of varying molecular weight); poly-
oxyl ethylene stearetes (also known as ethoxylated fatty acid
esters, macrogl stearetes, MARLOSS™, PEG fatty acid
esters, PEG stearetes, polyethylene glycol stearetes, poly
(oxy-1,2-ethanediyl) -1-hydroxy-1-hydroxystearate,
known as dodecyl sodium sulfate, ELFAN® monostearate, heavy mineral oil, PEG talline wax, 2.7% glyceryl monostearate, potassium (E,E)-sorbate; sorbic acid potassium salt; sodium lauryl sulfate (also known as dodecyl sodium sulfate, ELFIN® 240, sodium dodecyl sulfate, sodium laurilsulfate, sodium monododecyl sulfate, sodium monolauryl sulfate, TEXAPON® K12P); sorbitan esters (sorbitan fatty acid esters) (also known as Spans); stearic acid and its salts (also known as cetlyleic acid, crodacid, E570, EDENOR®, EMERSOL®, HYSTRENE®, INDUSTRENE®, KORTACID™ 1895, Pearl Steric, PRISTERENE®, stereophonic acid, Tegostearic); triethanolamine (also known as TEA, Tealan, triethyolamine, trihydroxyethylamine, tris (hydroxyethyl)amine); triethyl citrate (also known as citric acid ethyl ester, CITROFLEX® 2, CITROFOL™ AI, E1505, HYDAGEN® CAT, TEC).

The embodiments shown and described in the specification are only specific embodiments of the inventor who is skilled in the art and thus are not limiting in any way. Various changes, modifications, or alterations may be made or resorted to without departing from the spirit of the invention or the scope of the following claims. As only two examples, additional actives may be incorporated into the formulation to provide additional medicinal effects, and/or the formulation may be provided in another type of carrier for self-application to the orthodontic bracket.

What is claimed is:

1. A method of alleviating orthodontic discomfort in a patient in need thereof, the method comprising applying a pharmaceutically acceptable composition of a wax, from 0.01% to less than 15% of an analgesic/anesthetic agent, and up to 30% xanthum gum to provide to the patient under conditions to alleviate orthodontic discomfort for at least eight hours and up to 24 hours after the application.

2. A method of alleviating orthodontic discomfort in a patient in need thereof, the method comprising applying a pharmaceutically acceptable composition of wax, glyceryl monostearate, heavy mineral oil, PEG 1500, Tween 80, from 0.01% to less than 15% of an analgesic/anesthetic agent, and up to 30% xanthum gum.

3. A method of alleviating orthodontic discomfort in a patient in need thereof, the method comprising applying a pharmaceutically acceptable composition of 83% microcrystalline wax, 2.7% glyceryl monostearate, 1.0% heavy mineral oil, 5% PEG 1500, 5% analgesic/anesthetic agent, 0.3% Tween 80, and 3% xanthum gum, the composition applied to an oral mucosal surface of the orthodontic patient under conditions to alleviate the orthodontic discomfort.

4. A method of alleviating orthodontic discomfort in a patient in need thereof, the method comprising applying a pharmaceutically acceptable composition of 50%-99% microcrystalline wax, 0%-10% glyceryl monostearate, 0%-30% heavy mineral oil, 0%-30% PEG 1500, 0.01%-14.99% analgesic/anesthetic agent, 0%-10% Tween 80, and 0.1%-30% xanthum gum, the composition applied to an orthodontic bracket or brace of the orthodontic patient under conditions to alleviate orthodontic discomfort.

5. The method of claim 1, the composition comprising from 50%-99% microcrystalline wax.

6. The method of claim 1, the composition comprising up to 10% glyceryl monostearate.

7. The method of claim 1, the composition further comprising up to 30% heavy mineral oil.

8. The method of claim 1, the composition further comprising up to 30% PEG 1500.

9. The method of claim 1, the composition further comprising up to 10% Tween 80.

10. The method of claim 1, wherein the analgesic/anesthetic agent is benzocaine.

11. The method of claim 1, wherein the applying step applies the composition to an oral mucosal surface in a patient.

12. An extended release pharmaceutically acceptable composition comprising microcrystalline wax, glyceryl monostearate, heavy mineral oil, PEG 1500, Tween 80, less than 15.0% of an analgesic/anesthetic agent, and up to 30% xanthum gum, the composition having an in-vitro release of the analgesic/anesthetic agent of about 28% to about 56% over eight hours.

13. The method of claim 15, wherein the applying step applies the composition to an oral mucosal surface in a patient.

14. The composition of claim 15, the composition comprising from 50%-99% microcrystalline wax.

15. The composition of claim 15, the composition further comprising up to 10% glyceryl monostearate.

16. The composition of claim 15, the composition further comprising up to 30% heavy mineral oil.

17. The composition of claim 15, the composition further comprising up to 30% PEG 1500.

18. The composition of claim 15, the composition further comprising up to 10% Tween 80.

19. The composition of claim 15, wherein the analgesic/anesthetic agent is benzocaine.

20. The composition of claim 15, wherein the analgesic/anesthetic agent is benzocaine.