This invention relates to an improved medicinal composition adapted for use on the gingival and lip surfaces as well as on the mucosa of the buccal and oral cavity in general, said surfaces and mucosa being referred to herein as the "oral mucosa," in order to achieve relief of pain. In particular, it is concerned with the use of organic or inorganic water soluble salicylates, for example, choline salicylate, sodium salicylate, potassium salicylate, calcium salicylate and morpholine salicylate, dissolved in a special vehicle which modifies the penetration of the active moiety in order to permit the attainment of therapeutically significant blood levels and, at the same time, to permit high local concentrations of the active compound. It is by virtue of this special property of the absorption of the active moiety as well as the attainment of high local concentrations, that affords maximal pain relief with minimal amounts of the water soluble salicylate used. Thus, through this double action, the effective concentration of the therapeutically active substance of this new product is materially less than would be required to produce an equal pharmacologic effect through a systemic action.

Eruption of deciduous teeth in infants is often associated with much pain and suffering. The gingivae at the point of emergence of the new deciduous teeth, may become swollen, inflamed and sensitive to contact and pressure, thereby producing irritability, fretfulness, disturbed sleep and excessive salivation. On occasion, an eruptive gingivitis during teething may become complicated by the development of a hemorrhagic cyst which is visible in the area overlaying the emerging tooth. The infant's response depends largely upon the severity of the pain. In an article appearing in the Journal of Dentistry of Children (volume 19, page 127-132, 1952), it was reported that, "the emotionality of the baby between the ages of six months and 30 months may be traced by the cutting of teeth. Each new tooth is accompanied by some physical upset, even though it may be of a minor sort, and this predisposes the baby to general irritability." Deciduous teeth are twenty in number and first appear at six to eight months of age. The teething process lasts up to approximately 30 months of age and it appears that many infants are in need of some comfort of irritating symptomatology resulting from this physiologic process for approximately the first two and one-half years of their life.

Lancing the gingivae over the bulging, emerging tooth was a common practice for many centuries. During the 19th century, the practice of providing soothing powders and syrups containing various preparations of opium, such as tincture of opium, became common. In more recent years the use of sedatives, hypnotics and other analgesic substances have been suggested. These are generally frowned upon because of the high order of toxicity and addiction resulting from the injudicious use of these potent substances.

Present therapy appears to depend largely upon the severity of the accompanying symptomatology. Small doses of sedatives and hypnotics, by a physician control, have been utilized. Local massage with aromatic compounds as well as the application to the gingival surface of small doses of alcohol has also been suggested. Where the discomfort and irritability are more pronounced, chloral hydrate, a powerful hypnotic, has been utilized. The use of the more potent local anesthetic compounds have been deplored because of their pronounced tendency to cause allergic reactions.

Painful conditions peculiar to the gingivae and mucosal membranes in and about the oral cavity are well known. Relief of pain associated with these conditions has been an especially difficult problem. Thus, the commonly practiced dental, surgical procedure of multiple extraction of diseased teeth has created problems of effective pain control during the post-operative period. A wide area of gingival tissue becomes painful and generally exhibits a local inflammatory response to the surgical trauma. When a large number of teeth are extracted at one time, the practice of suturing the wound in order to prevent excessive bleeding, gives rise to prolonged pain during the postoperative period. This practice is further complicated by other advances in dental science which now permit the immediate insertion of new dentures after surgery. It is an extremely difficult process to achieve pain relief in these conditions. Local anesthetic agents are generally not utilized because of their relatively short period of activity as well as the great danger of allergic reactions arising from their multiple use.

The modern use of artificial dentures to replace missing or extracted teeth is another cause of painful conditions of the mouth. A new dental technique permits the denture to be inserted into the patient's mouth as soon as the teeth have been extracted, and this technique is known as "immediate denture method." Under this practice, the gums are sutured after extraction of the teeth in order to lessen the healing time required as well as to prevent excessive blood loss and the previously prepared denture is immediately inserted. It is the usual practice to permit this denture to remain in the mouth substantially continuously during the first seventy-two hour period subsequent to extraction in order to minimize the excessive swelling of the gingival tissue and to insure that healing will take place in the same contour as had previously existed. Maintaining these artificial dentures during the first seventy-two hours is often a painful experience.

A similar problem exists with the older procedure of utilizing dentures to replace missing teeth. These are inserted four to six weeks after the extraction of teeth, subsequent to substantial healing of the alveolar ridges of the gums. These new dentures often result in pain to the patient during the initial period of adaptation since it is virtually impossible to prepare a prosthetic appliance which corresponds exactly to the contour and shape of the gingival surface.

Still another painful condition arises in the oral cavity which involves the oral mucosal membranes and these are those local inflammations and abraded areas as a result from certain infections, for example, the common cold sore, the fever-blisters or herpes simplex, which arises predominantly on the lips. Included among these painful conditions are mechanical irritations resulting from accidental biting of the internal membranes of the mouth and also local infections of the mucosal surface, per se.

Relief of pain may be achieved through four fundamental methods. These are: (a) removing the underlying cause of the pain; (b) blocking the pathway of the painful impulses; (c) raising the pain threshold by suppressing the pain reaction by depressing the cortical area of the brain. The removal of the cause of the pain is the most desirable method of pain relief, but this is not always possible. Thus, pain, after surgery, arises from the trauma to the tissues and will disappear when this injury has been resolved. During this period of time, however, pain will be present as a natural consequence to surgery. On the other hand, in certain infectious states, the pain may be relieved to a very great degree.
merely by controlling the infection or by providing adequate drainage to the area. It should be recognized that pain during the postoperative phase is a necessary adjunct to the surgery and requires special techniques for effective control.

Blocking the pathway of the painful impulse is perhaps the most widely used method to manage pain arising in and about the buccal cavity. The use of local anesthetics which are injected into the tissue about the nerve is the accepted and most common anesthetic procedure for dental surgery pain control. Although local anesthetics are used almost exclusively for the operative period and have, on occasion, been used for acute painful states because of their short period of pain relief, these agents do not lend themselves to continuous or multiple and repeated applications.

The use of large amounts of systemic analgesics to depress the pain reaction has as its principal drawback, the fact that a general systemic effect is achieved when only a local action is desired. Thus, it is unwise to dull the perception of the patient as well as to subject the cardiovascular, renal and pulmonary systems to the depressant effects of an analgesic, sedative or hypnotic agent when effective pain control may be achieved by local application.

Although the raising of the pain threshold will generally involve a central nervous system effect, this may also be achieved by modifying or altering the response at the peripheral or cellular level. Thus, the application of topical local anesthetic renders the area insensitive to pain by blocking the perception of these painful stimuli. While this may be considered to be a special form of nerve blockade, it is generally recognized that the essential physiology of nerve transmission remains intact although the response of the nerve endings in their sensitivity to painful stimuli, has been altered.

It is, therefore, evident that pain arising from the mucosal and gingival tissue in and about the oral or buccal cavity may result from a multiplicity of causes. Nevertheless, the approach to the management of these painful states is the same despite the variety of causes. We have found that the application of the product of the present invention to the surface of the buccal mucosa and gingival tissue in and about the mouth, will result in a prompt relief of these painful states without disagreeable or unwanted side reactions. A particular advantage of the use of the product of this invention is that it will provide effective pain relief to these common and distressing painful symptoms by selectively rejecting the patient to the noxious effects of large quantities of systemically acting analgesic agents, nor does this product influence the functioning of the cardiovascular system, the renal system and central nervous system as would be observed after the use of narcotic, sedative and tranquilizing medications. This new material may be used for infants. No allergic side reactions have been reported.

We have found that the application of a water soluble salicylate in an aqueous alcoholic and hydroalcoholic gel, wherein the concentration of the salicylate ion is from 2 to 10 percent and the whole buffered to a range of from pH 4 to pH 7, will cause prompt, effective relief of pain. Unexpectedly, this result occurs despite the fact that the concentration of salicylate ions is far below that required to exert an effect or to produce significant elevations in the blood level of salicylate ions when the active compound is administered either orally or rectally. This high degree of pain relief is achieved because of the particular action of this form of salicylate ions in the specially buffered media, which permits the attainment of maximal local cellular concentrations of the salicylate ion while, at the same time, permitting absorption in order to obtain benefit of systemic analgesia.

These unique actions of the invention we describe sharply distinguish it from the water insoluble salicylates such as aspirin and salicylic acid that have frequently been used in attempts to obtain relief from painful conditions in the mouth through their local application. Thus, the authoritative Second Edition of "Pharmacology in Medicine" edited by Victor Drift, Ph.D., M.D., at page 293 states, "Careful studies in man have shown that when aspirin is placed in the mouth absorption is negligible if the patients are warned not to swallow their saliva."

Since it is obviously very difficult to make certain that a patient does not swallow his saliva and thus enable a salicylate originally present in his oral cavity to be absorbed via the stomach, the unique property of our invention was demonstrated as follows: Five ml. of a hydroalcoholic gel containing 436 mg. choline salicylate were placed in the buccal cavity of each of two anesthetized rabbits in whom the esophagus had previously been ligated to prevent accidental swallowing of the preparation and in whom a tracheal cannula was inserted both to provide proper ventilation and to insure that none of the preparation could be aspirated into the bronchial tract from which it might be absorbed. Blood samples were withdrawn at 5, 15, 30, 60 and 120 minutes and the plasma salicylate levels determined by conventional techniques. The results, as indicated in Table I, demonstrate rapid absorption of salicylate from the mouth, as present in this preparation.

<table>
<thead>
<tr>
<th>Blood Sample</th>
<th>Plasma Salicylate Levels, mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit #1</td>
<td>Rabbit #2</td>
</tr>
<tr>
<td>5 min.</td>
<td>9</td>
</tr>
<tr>
<td>15 min.</td>
<td>7</td>
</tr>
<tr>
<td>30 min.</td>
<td>5</td>
</tr>
<tr>
<td>45 min.</td>
<td>4</td>
</tr>
<tr>
<td>60 min.</td>
<td>3</td>
</tr>
<tr>
<td>90 min.</td>
<td>3</td>
</tr>
<tr>
<td>120 min.</td>
<td>3</td>
</tr>
</tbody>
</table>

The equally authoritative Second Edition of "The Pharmacological Basis of Therapeutics" by Louis Goodman, M.D., and Alfred Gilman, Ph.D., at page 284 states, "The use of aspirin locally for alleviating dental pain or sore throat has no rational basis." As will be demonstrated, the use of the type of hydroalcoholic gel described above in actual clinical trials does provide effective relief from such pain.

Any water soluble salicylate, as for example, choline salicylate, potassium salicylate, sodium salicylate, calcium salicylate, morpholine salicylate may be used to achieve this effect. In practice, it has been found that choline salicylate is a preferred compound. When choline salicylate is used to achieve the pain relief in and about the oral cavity, an optimal concentration will be approximately 7.5 percent with an effective range of from 2 to 10 percent. The preferred pH for the preparation containing choline salicylate is between pH 5.5 and pH 6.5, although a pH range of 4 to 7 may be employed. The preferred dosage form is a hydroalcoholic gel although an aqueous gel may be used.

In preparing an aqueous gel or hydroalcoholic gel to be used as a vehicle for the salicylate ion, there may be employed such gelling agents as methyl cellulose, methylcellulose, polyoxyethylene glycol, polyvinyl pyrrolidone, dextran, gum guar, algin gum, gum acacia and gum tragacanth. A preferred gelling agent is methyl cellulose.

The preparation known as "Methocel-4000," a proprietary form of methyl cellulose, has been found particularly useful. This form has a viscosity of 4000 centipoises when a 2 percent aqueous solution is maintained at 20° C.

The concentration of the gelling agent ranges from 0.1 to 4 percent, depending upon the desired viscosity of the finished gel as well as the physical properties of the particular gelling agent selected.

The gel is prepared by dispersing the gelling compound in the selected menstrum which may be water or hydro-
alcoholic solutions containing from 10 to 60 percent of alcohol, containing the appropriate quantity of the selected water-soluble salicylate and the pH adjusted, if necessary, to the desired range. The finished gel may be flavored with appropriate aromatic substances.

An antiseptic may be incorporated into the gel and compounds such as cetyltrimethylbenzylammonium chloride, in concentrations of from 0.005 to 0.05 percent; penicillin and penicillin salts, from 100,000 to 1 million units per gram; tetracycline, from 2 to 5 mg. per gram; tetrycline, from 5 to 15 mg. per gram and neomycin, 5 mg. per gram, may be utilized.

A preferred effective formulation of the choline salicylate gel preparation is as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline salicylate</td>
<td>8.72</td>
</tr>
<tr>
<td>Cetyltrimethylbenzylammonium chloride</td>
<td>0.01</td>
</tr>
<tr>
<td>Methylcellulose-4,000</td>
<td>2.75</td>
</tr>
<tr>
<td>Glycerine</td>
<td>5</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>39.16</td>
</tr>
<tr>
<td>Oil of anise</td>
<td>0.143</td>
</tr>
<tr>
<td>Menthol</td>
<td>0.057</td>
</tr>
<tr>
<td>Cyclohexylsulfamic acid</td>
<td>0.2</td>
</tr>
<tr>
<td>Water—q.s.d.</td>
<td>100</td>
</tr>
</tbody>
</table>

The glycerine is combined with the alcohol and the cyclohexylsulfamic acid, menthol and oil anise is dissolved in the solution. The cetyltrimethylbenzylammonium chloride is dissolved in approximately three-fourths of the required volume of water and when solution has been achieved, the methylcellulose is dispersed in the aqueous solution and the choline salicylate added. The alcoholic solution is then mixed with the aqueous solution while stirring and the whole gently warmed to about 50° C. and filtered. The solution is brought to proper volume with additional quantities of water. On cooling, a clear viscous gel forms which is suitable for application to the painful area.

A number of clinical studies evaluating the degree of pain relief afforded by the application of the product of the present invention to the mucosa of the oral cavity in more than 350 infants patients, established the desirable beneficial properties of this new preparation. All of the patients evidenced painful and distressing disturbances which accompanied the teething process. The most common symptoms reported were crying, irritability, redness, fever, refusal to eat, sleeplessness at night, drooling and thumb-sucking. Some of the patients presented the more severe symptoms of anorexia, vomiting and diarrhea.

After application of the choline salicylate gel to the gingival surface, prompt effective pain relief was observed and results of the study of 387 patients were classified as good to excellent in 339 infants or 87.6 percent of the group studied. The results were fair for 12 patients and there was a poor response observed in 36 patients (9.3%).

The acceptance of the preparation by the patient was unanimously favorable and this included a group of 11 infants in whom the gel remained in contact with the gingival surface for an extended period of time.

In another study the effect of the choline salicylate gel for the relief of pain associated with dentition in infants, evaluated by a double-blind technique, in which a group of 28 infants of from 4 to 15 months of age were treated with the "active teething-gel" of the present invention, and a control group of 21 infants of a similar age distribution were treated with a placebo or "inactive gel" preparation. All of the infants showed objective signs of distress such as fretfulness, drooling and crying before the study was started and about one-third of the group refused food, while two-thirds of the group had gingival hyperemia, two-thirds, a gingival edema and of this latter group, one-third showed findings of both.

A small portion of a coded test preparation was carefully massaged onto the infants gums and this was repeated three to four times daily as long as there were recurring signs of distress. The mothers were instructed to time the latent period between successive applications and apparent relief onset. The results of the study indicated that the active teething gel preparation was effective to an excellent degree in 23 patients or 82 percent, and to a good degree in 9 patients or 18 percent. There were no failures in this test group. In contrast to this finding, the placebo medication afforded the following results: 7 patients, excellent; 7 patients, good and 7 patients, poor.

There were no side reactions observed in any of the patients of either group.

The latent period between the application of the active gel and apparent effect was from 5 to 30 minutes with an average of 16 minutes. In three cases, the latent period was 30 minutes and in 15 instances it was 10 minutes while in three patients it required five minutes for the onset of effective pain relief. Among the placebo reactors, only the 7 excellent responses were observed to have an effect within 30 minutes while the 7 with good results required a latent period of between 45 minutes and 1 hour.

The following examples illustrate the scope of this invention:

Example 1

To prepare the analogical gel, choline salicylate, 8.72 gm. and cetyltrimethylbenzylammonium chloride, 0.01 gm. are added to 39.16 gm. of ethyl alcohol. To this solution is added 0.143 gm. of oil of anise, 0.057 gm. of menthol and 0.2 gm. of cyclohexylsulfamic acid. The mixture is stirred until complete solution is achieved. In a separate flask containing 40 ml. of distilled water, is dispersed 2.75 gm. of methyl cellulose—4,000, and the dispersion heated to 50° C. To this mixture is added 5 gm. of glycerin. The aqueous dispersion of the gelling agent is added slowly, with constant stirring, to the warmed (to 40–50° C.) alcohol solution prepared earlier. The mixture is filtered and the pH of the solution determined. The pH is then adjusted to pH 6 with choline base, or with salicylic acid, depending on whether the original pH of the mixture is greater or lesser than pH 6. The dispersion is then brought to proper volume, 100 gm., with distilled water, and allowed to cool. On cooling the mixture forms a semisolid gel, suitable for application to the oral mucous. Of course, if more pain relief is sought, the antiseptic may be omitted.

Example 2

In place of the choline salicylate used there may be substituted any water soluble salicylate, as for example, sodium salicylate, potassium salicylate, calcium salicylate and morpholine salicylate, in a concentration of from 2 to 10 percent by weight of salicylate ion of the quantity of gel prepared. If necessary, the pH of the gel should then be adjusted to approximately pH 5–7 by the addition of the required amount of non-toxic acid or base.

Example 3

In place of the methyl cellulose—4000 used in Example 1, may be substituted the following gelling agents in the respective percentage quantities noted: gum guar, from 0.5 to 3 percent; methylcellulose, from 0.1 to 3 percent; polyoxyethylene glycol, from 0.1 to 4 percent; polyvinyl pyrrolidone, from 1 to 4 percent; dextran, from 0.5 to 4 percent; algin gum, from 0.5 to 3 percent; gum acacia, 0.5 to 5 percent and gum tragacanth, from 0.5 to 3 percent. The remainder of the steps being the same.

Example 4

In place of cetyltrimethylbenzylammonium chloride used in Example 1 there may be substituted, in respective amounts, such germicidal substances as: penicillin and penicillin salts in concentration of from 100,000 to 1 million units per gram of preparation; tyrothricin, from 2 to 5 mgm. per gram of preparation; tetrycline, from 5 to 15 mg. per gram of preparation; and neomycin, 5 mg.
per gram of preparation. These antibiotic substances are added after the solution has been filtered, but prior to the adjustment of pH and volume. The remainder of the steps being the same.

Example 5

When it is desired to obtain relief of pain arising from the gingival mucosa or the oral mucosa, a small amount of gel containing the water soluble salicylate is applied to the affected area, from one to six times daily, depending upon the severity of the pain. Gentle massage is used to assure penetration, and an even distribution. A prompt relief of pain results after application. In applying the gel to relieve the pain resulting from new dentures, a small amount of the gel is applied directly to the gingival surface and an additional quantity may be distributed over the surface of the denture, coming in contact with the gingival tissue. The applications may be repeated as often as is necessary although from 1 to 6 times daily is the preferred regimen. When it is desired to treat the common “cold sore” or “fever blister” a small amount of the gel is applied directly to the affected area. Pain relief will be prompt without a “numbing” sensation and the applications of the agent may be repeated from 1 to 4 times daily.

What is claimed is:

1. An analgesic preparation for the application to the oral mucosa, comprising a gel selected from the group consisting of aqueous and hydroalcoholic gels and a water soluble salicylate compound dissolved in said gel, said preparation having a pH of from pH 4 through pH 7 and the salicylate ion content of said compound being from 2 percent to 10 percent by weight of said preparation.

2. An analgesic preparation for application to the oral mucosa, comprising a gel selected from the group consisting of aqueous and hydroalcoholic gels and choline salicylate dissolved in said gel, the salicylate ion content of said choline salicylate being from 2 percent to 10 percent by weight of said preparation and the pH of said preparation being from pH 4 through pH 7.

3. An analgesic preparation for application to the oral mucosa comprising a gel selected from the group consisting of aqueous and hydroalcoholic gels and morpholine salicylate dissolved in said gel, the salicylate ion content of said morpholine salicylate being from 2 percent to 10 percent by weight of said preparation and the pH of said preparation being from pH 4 through pH 7.

4. An analgesic preparation for application to the oral mucosa comprising a gel selected from the group consisting of aqueous and hydroalcoholic gels and sodium salicylate dissolved in said gel, the salicylate ion content of said sodium salicylate being from 2 to 10 percent by weight of said preparation and the pH of said preparation being from pH 4 through pH 7.

5. The method of achieving oral mucosal analgesia which comprises applying to the oral mucosa of a human the preparation described in claim 1.

6. The method of achieving oral mucosal analgesia which comprises applying to the oral mucosa of a human the preparation described in claim 2.

7. The method of achieving oral mucosal analgesia which comprises applying to the oral mucosa of a human the preparation described in claim 3.

8. The method of achieving oral mucosal analgesia which comprises applying to the oral mucosa of a human the preparation described in claim 4.

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