United States Patent [19]

Loesche

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[54] **COMPOSITION FOR PERIODONTAL ADMINISTRATION**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 405,790, Aug. 6, 1982, abandoned.

[51] **Int. Cl.**[4] **A61K 9/22;** A61K 9/52

[52] **U.S. Cl.** **424/19;** 514/365; 424/28

[58] **Field of Search** ..... 424/22, 26, 28, 19, 424/273 R, 52; 106/35; 514/365

[56] **References Cited**

PUBLICATIONS

Soskolne et al., New Sustained Release Dosage Form of Chlorhexidine for Dental Use, J. Perio, Res, 18:330–336.

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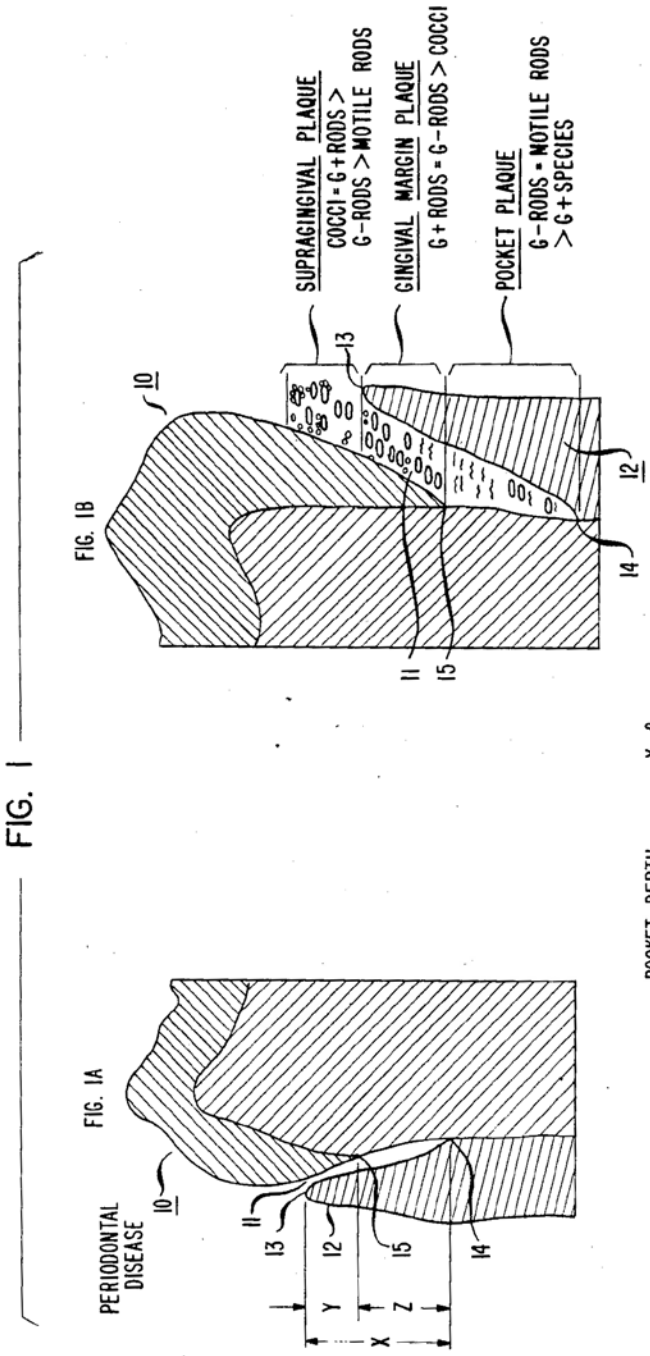
Assistant Examiner—C. Joseph Faraci

[57] **ABSTRACT**

A composition for periodontal administration and a method of periodontal treatment involving a slow release device which can be placed directly into the periodontal pocket where metronidazole, with or without antioxidants, are released over periods of days to weeks at a cidal concentration for anaerobes in the domain of the periodontal pocket.

2 Claims, 3 Drawing Figures



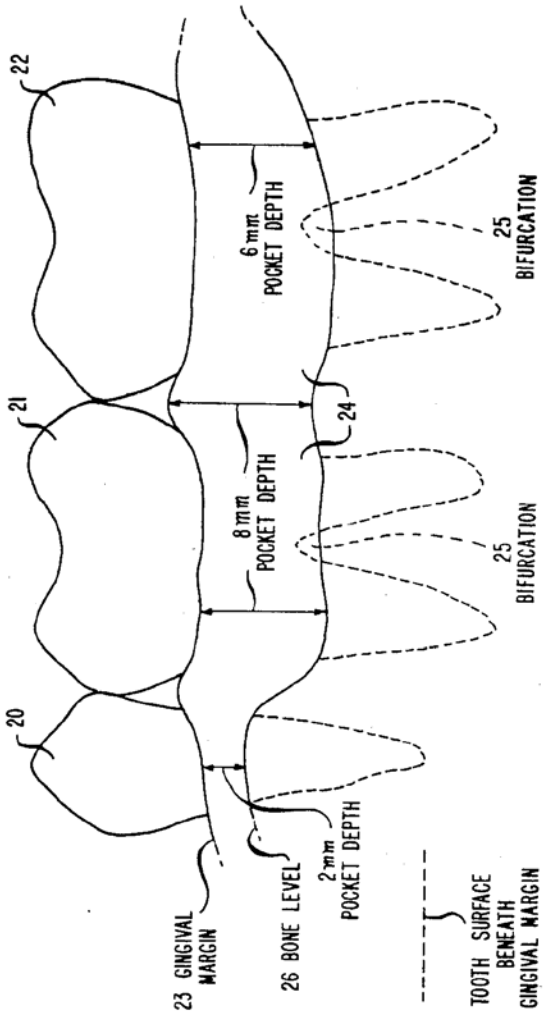


FIG. 2

PROFILE OF THREE TEETH SHOWING POCKET DEPTH AS DISTANCE BETWEEN GINGIVAL MARGIN 23 AND BONE LEVEL 26. NOTE THAT DEEP POCKETS (6 TO 8 MM IN DEPTH) ARE ABOUT THE FIRST AND SECOND MOLARS (TEETH 21 AND 22).

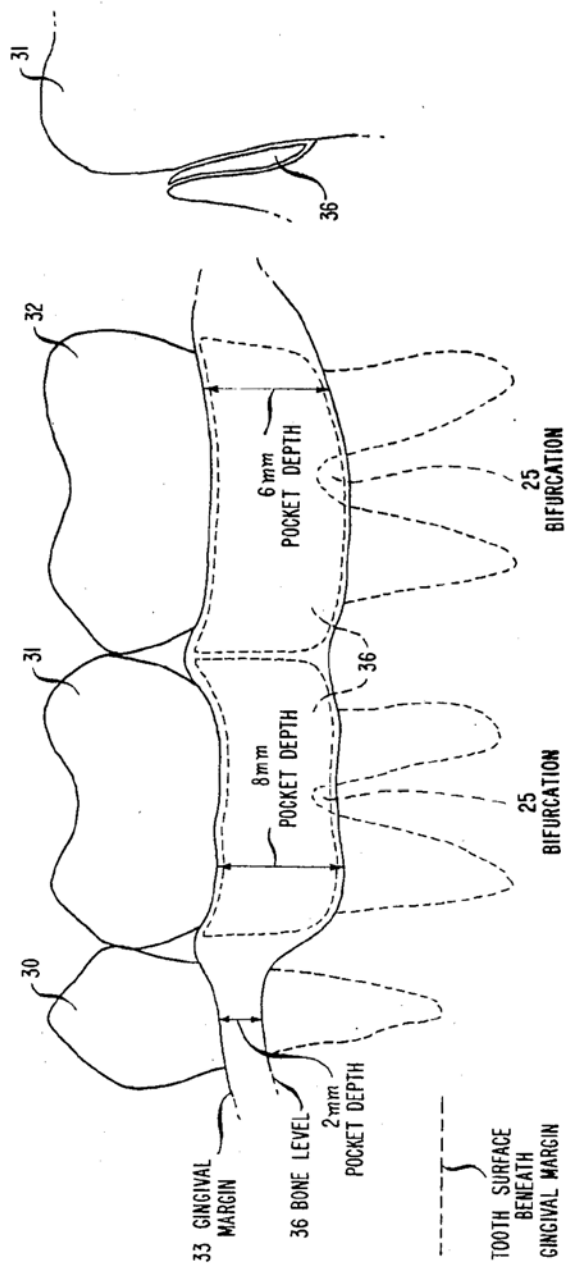


FIG. 3

PROFILE OF THREE TEETH SHOWING TWO CONTOURED DRUG RELEASING FILMS 36 SUBGINGIVALLY PLACED ONLY IN THOSE SITES WHERE THE POCKET DEPTHS ARE 6 MM OR MORE. NOTE THAT THE FILMS CAN BE PLACED OVER THE BIFURCATION SITES 25.

COMPOSITION FOR PERIODONTAL ADMINISTRATION

CROSS-REFERENCES

This is a continuation-in-part of Ser. No. 405,790 filed 8/6/82 now abandoned.

BACKGROUND OF THE INVENTION

1. Technical Field

This invention relates to a composition for periodontal administration that is cidal for anaerobes in the domain of the periodontal pocket and to a novel method of treatment of anaerobic infections in periodontal disease that is dependent upon the slow release of metronidazole from a plastic film that is placed within the periodontal pocket, and which film resides in such pocket for a period of days to weeks.

2. Description of Prior Art

The main cause of tooth loss in adults is periodontal disease. Yet, surprisingly, less than one percent of the public expenditures for dental treatment is for periodontal disease (see J. Dent. Educ. 43:320, (1979). This is because conventional periodontal treatment is too expensive for most individuals, mainly due to the labor intensive, symptomatic treatment that is usually performed by highly skilled specialists.

Periodontal disease is an all-inclusive term for a variety of clinical entities that are forms of either gingivitis or periodontitis. Gingivitis is an inflammation of the gingiva or gums that can be associated with poor oral hygiene and/or hormonal states of the host. It is assumed, but not proven in the human, that gingivitis will progress to a periodontitis, which is the form of the disease in which the infection has progressed to involve the oral tissues which retain the teeth in the jaw bone. Periodontitis is the more severe form of the disease, and if untreated, will eventuate in the loss of the tooth.

Dentists have long assumed that periodontal disease originates by the overgrowth of bacteria on the tooth surfaces in aggregates known as dental plaque. If this plaque persists for long periods of time on the tooth surfaces, it may in some instances calcify, forming the hard substance known as calculus. Numerous studies describe chemical agents which can in vitro and in vivo reduce plaque formation and calculus. However, none of these chemical agents has been reported to be successful in treating periodontitis.

A substantial number of different types of compounds and compositions have been developed for use as antibacterial and antiplaque agents, e.g., benzethonium chloride and cetyl pyridinium chloride, disclosed in U.S. Pat. No. 4,110,429, or as anticalculus agents, e.g., 2-phosphono-butane 1,2,4-tricarboxylic acid, disclosed in U.S. Pat. No. 4,224,308. These compounds are designed to be used by the individual in dentifrices, dental powders, pastes, mouthwashes, nonabrasive gels, chewing gums, topical solutions and the like, e.g., see U.S. Pat. No. 4,205,061. They are designed to be used as prophylactic agents, usually without requiring a prescription or supervision during usage, e.g., see U.S. Pat. No. 4,251,507. Often they are compounded with detergents and other cleaning agents, and this cleaning action is often an important aspect of the invention, e.g., see U.S. Pat. Nos. 4,251,507 and 4,205,061. None of these compounds or compositions are designed to be used as antimicrobial agents for the treatment of periodontitis, nor are they formulated to be slow release devices for these antimicrobial agents in vivo.

Recent research in periodontal disease (see, for example, Chemotherapy of Dental Plaque Infections, Oral Sci. Rev. 9:65–107, 1976) indicates that gingivitis and periodontitis are characterized by different types of bacteria. Gingivitis is associated with the accumulation of gram positive cocci and actinomyces, whereas periodontitis is characterized by proportional increases in anaerobic bacteria, such as spirochetes and black pigmented bacteroides (see Host-Parasite Interactions in Periodontal Disease. R. J. Genco and S. E. Mergenhagen, eds. Amer. Soc. for Microbiol. Washington, D.C. p. 27–45, 62–75, 1982). The different bacterial compositions of plaque associated with either gingivitis or periodontitis suggest that a mode of treatment that is effective in gingivitis may not be effective in periodontitis. This is an important factor in the present invention, as previous discoveries in the area of periodontal disease have assumed that there is no bacterial specificity in periodontal disease. This is now known to be incorrect. These bacterial differences in plaque may explain why an agent effective in plaque control, such as chlorhexidine, has little effect on gingivitis and no published effect on periodontitis.

Another important finding from recent periodontal research is that the composition of the dental plaque will differ according to its location on the tooth surface. Above the gingival or gum margin, facultative bacteria, such as gram positive cocci and rods, are numerically dominant, whereas below the gum margin, anaerobic motile bacteria such as spirochetes, and anaerobic gram negative rods including the black-pigmented bacteroides are predominant. In other words, two different microbial ecosystems are present on the same tooth surface.

This is illustrated in the accompanying drawings in FIGS. **1***a* and **1***b*, which show a cross section of a tooth **10**, a periodontal pocket **11**, and the gingiva or gum **12**. The tooth illustrated in FIG. **1***a* exhibits periodontal disease in which periodontal attachment of the tooth to the alveolar bone has been destroyed, and a periodontal pocket **11** has been formed between the gum **12** and the root surface of the tooth. Clinical assessment of such deterioration of teeth is made by measuring the depth of the pocket. This is done by inserting a periodontal probe or ruler, a thin metal rod (not shown), to the base of the pocket **14**. Two measurements can be obtained with the probe. One, called the pocket depth x, in illustration **1***a* is the distance between the height of the gingival margin **13** to the base of the pocket **14**. The other measurement, y, is the distance between the height of the gingival margin **13** and the cementoenamel junction (CEJ)**15**. The CEJ is extremely valuable because it gives a permanent reference mark on each tooth surface from which one can base further measurements. It enables one to divide the pocket depth measurement into two components: the distance between the CEJ and the top of the gingival margin, y, and the distance between the CEJ and the bottom of the pocket, z. This letter measurement is called the attachment distance. As illustrated in the diseased tooth, the attachment distance is 5 mm and the pocket depth is 8 mm.

FIG. **1***b* is an enlargement of a section of the type shown in FIG. **1***a* in which the periodontal pocket **11** is now filled with bacterial plaque. Note that the plaque lies between the tooth and the gingiva in the space

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