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Desensitizing teeth with degradable particles

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<b>(21) International Application Number:</b> PCT/US95/14670 <b>(22) International Filing Date:</b> 9 November 1995 (09.11.95) <b>(30) Priority Data:</b> 336,486 9 November 1994 (09.11.94) US <b>(60) Parent Application or Grant</b> (63) Related by Continuation US 336,486 (CON) Filed on 9 November 1994 (09.11.94) <b>(71) Applicant (for all designated States except US):</b> GILLETTE CANADA INC. [CA/CA]; 16700 Trans Canada, Kirkland, Quebec H9H 4Y8 (CA). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MASTERMAN, Thomas, Craig [US/US]; 35 Myrtle Street #3, Boston, MA 02114 (US). SPENCER, Jean, L. [US/US]; 19 Middle Street #4, Boston, MA 02127 (US). <b>(74) Agents:</b> HANDELMAN, Joseph, H.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.	<b>(81) Designated States:</b> AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(54) Title:</b> DESENSITIZING TEETH WITH DEGRADABLE PARTICLES		
<b>(57) Abstract</b>		
A method for desensitizing a hypersensitive tooth in a patient includes contacting exposed tubules with particles including a degradable material.		

DESENSITIZING TEETH WITH DEGRADABLE PARTICLES

The invention relates to desensitizing teeth.

The dentin layer in a tooth generally contains channels, or tubules, extending from the pulpal surface to the peripheral surface located underneath the enamel and cementum. Loss of enamel and/or gingival recession accompanied by loss of cementum may expose these tubules in the dentin. It has been theorized that these exposed tubules are responsible, in part, for hypersensitivity to mechanical pressure or hot or cold fluids.

The problem of hypersensitive teeth is well-recognized, and various treatments have been proposed in the art. Pashley et al., U.S. Pat. No. 4,057,021, describes desensitizing hypersensitive teeth by applying an aqueous solution of alkali metal salts and ammonium oxalate to the surface of the teeth. Kim, U.S. Pat. Nos. 4,631,185 and 4,751,072 describes desensitizing teeth by treatment with potassium salts. Neirinckx, U.S. Pat. No. 4,990,327, describes desensitizing teeth with strontium ion and fluoride ion. Mason, U.S. Pat. No. 4,992,258, describes desensitizing teeth by applying a dentifrice including a montmorillonite clay. Lutz, U.S. Pat. No. 4,011,309, describes a desensitizing dentifrice composition that includes citric acid, sodium citrate, and non-ionic polyol surfactant. Mlkvy et al., U.S. Pat. Nos. 3,888,976 and 3,772,431 describe using a zinc or strontium ion containing astringent-desensitizing agent in an effervescent mouthwash tablet. Hodosh, U.S. Pat. NO. 3,863,006, describes desensitizing teeth with a nitrate salt. Svajda, U.S. Pat. No. 3,689,636, describes desensitizing teeth with solutions of chloride salts. Rosenthal, U.S. Pat. No. 3,122,483,

describes desensitizing teeth with strontium ions. Scheller, US Pat. Nos. 4,634,589 and 4,710,372, describe a dentifrice containing apatite particles for treating hypersensitive teeth. Turesky *et al.*, US Pat. No. 5,250,288, describes desensitizing a hypersensitive tooth by treating the surface of the tooth with charged polymeric particles.

5 According to a first embodiment of the invention there is provided a method for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said method comprising contacting said exposed tubules with particles, comprising a degradable material, as herein defined, that are sufficiently small to block or clog said dentin tubules in an amount effective to desensitize said tooth.

10 According to a second embodiment of the invention there is provided the use of particles comprising a degradable material, as herein defined, for the preparation of a formulation for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said particles being sufficiently small to block or clog said dentin tubules in said hypersensitive tooth.

15 According to a third embodiment of the invention there are provided particles comprising a degradable material, as herein defined, when used for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said particles being sufficiently small to block or clog said dentin tubules.

The invention features a method for desensitizing a hypersensitive tooth in a patient.

20 The method includes contacting the tubules exposed on the surface of a hypersensitive tooth with particles that contain a degradable material. The particles block or cover the tubules in the dentin layer, which results in desensitization. Importantly, particularly when the particles are composed substantially only of the degradable material, for the most part nothing remains of the particles in the mouth or body once the degradable material degrades.

25 The preferred particles have an average size of between 0.01 micron and 3 microns, more preferably between 0.2 micron and 0.6 micron. The particles may be microspheres, and may have a charged outer surface that help the particles cling to the surface of the tooth and block the exposed tubules. The preferred particles optionally may include an antimicrobial agent absorbed on the surface, as described in US. Pat. No. 5,300,290, or dispersed throughout the particles, as described in USSN 08/322,926, filed October 13, 30 1994, which is assigned to the same assignee as the present application. The preferred particles also optionally may include an analgesic compound (e.g., benzocaine, barbital), which can be absorbed on the outer surface of the particle as described in US Pat. No. 35 5,252,577, or dispersed throughout the article. These



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patents and patent application are incorporated by reference herein.

In a preferred method, the surface of the hypersensitive tooth is polished, and a dispersion of the particles is applied to the polished surface for at least one minute. A preferred method of applying the particles is by brushing the teeth with a toothbrush having bristles that include the particles.

Some preferred particles are stable when stored, e.g., as an aqueous dispersion, because the preferred particles have non-porous water-stable exteriors composed of a water-stable material. Some preferred water-stable materials are disrupted by mechanical stresses, such as chewing, flossing, and brushing. Such water-stable materials include hydrophobic materials like poly(methyl methacrylate), polystyrene, beeswax, carnauba wax, petroleum wax, and similar materials which do not significantly degrade when exposed to oral enzymes. Other preferred water-stable materials degrade when exposed to oral enzymes. Such materials include polyhydroxyalkanoic acids, glycolipids, glycerides, and phospholipids.

In some preferred embodiments, the water-stable material functions as both a degradable material and a water-stable exterior coating. A particularly preferred material for this embodiment is glycerol distearate.

Preferred degradable polymers include polyglycolic acid, polylactic acid, and copolymers of glycolic acid and lactic acid, and esters of glycerol like glycerol distearate.

"Degradable material", as used herein, means a material which degrades within three months when placed in the mouth of a typical patient. The materials degrade as a result of exposure to one or more enzymes that commonly are

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found in the mouth. These enzymes include lipases, proteases, and glucosidases. Specific enzymes include parotid amylase, hyaluronidase, beta-glucoronidase, chondroitin sulfatase, amino acid decarboxylases, catalase, 5 peroxidase (such as lacto peroxidase), collagenase, and lysozyme.

"Water-stable exterior", as used herein, means that the exterior surface of the particle is composed of a material that does not chemically degrade or swell when 10 exposed to water. For example, as a result of the water-stable exterior, if the particle includes an anti-microbial agent or an analgesic, substantially no (i.e., less than 5% by weight) anti-microbial agent or analgesic leaches from the particle when the particle is placed in distilled water 15 (at a concentration of 10% of the dispersion by weight) at room temperature for a month.

The invention provides an effective, straightforward way to desensitize teeth. Without being bound to any theory, it is believed that the invention is effective at 20 least in part because the particles block the tubules in the teeth, making it more difficult for external stimuli like hot or cold temperatures to affect the nerve in the pulp. When some of the particles blocking the tubules eventually wash out of the tubules or degrade, they are easily 25 replenished by an additional application of particles.

Other features and advantages of the invention will be apparent from the description of the preferred embodiment thereof, and from the claims.

FIGS. 1a and 1b are electron micrographs of a dentin 30 surface prior to exposure to the particles of the invention.

FIGS. 2a and 2b are electron micrographs of a dentin surface after exposure to the particles of the invention.

The more preferred particles have an average diameter of less than 0.6 micron. Larger particles may not fit as well in dentin tubules, and as a result may not be as effective at blocking the tubules and desensitizing the  
5 teeth.

The particles include a degradable material. Preferred degradable materials include polycaprolactone, polydecalactone, poly(sebacic anhydride), sebacic acid-co-1,3-bis(carboxy-phenoxypropane), sebacic acid-co-1,6-  
10 bis(carboxyphenoxy-hexane), dedecanoic-co-1,3-bis(carboxyphenoxypropane), dedecanoic-co-1,6-bis(carboxyphenoxyhexane), albumin and derivatives, gelatin and derivatives, starch and derivatives, gum arabic, cellulose and derivatives, polysorbate and derivatives,  
15 agarose, lectins, galactose, functionalized nylons (e.g. benzylated), proteins (synthetic and natural), polyorthoesters, polyorthoformate, polyureas, polyurethanes, poly(amide-enamine)s, polyvinylalcohol, polyenolketone (PEK), polyHema, functionalized polyHema, ethylene-  
20 vinylacetate copolymers, functionalized polymers and copolymers of lactic and glycolic acid, lactic acid homopolymer, glycolic acid copolymer, copolymers of lactic acid and glycolic acid, polyhydroxybutyrate, poly(ester-imides), functionalized silicones, poly(anhydrides),  
25 poly(malic acid), and polyhydroxyalkanoic acids from synthetic or natural sources (eg., bacterial, fungi and the like).

Other preferred degradable materials include monomeric species and mixed monomeric/polymeric species such  
30 as liposomes, glycolipids, fatty acids, glycerides, carnauba wax, and phospholipids. The degradable materials can be included in organic/inorganic composites (covalent or mixed)

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by combining any of the polymers listed above with minerals such as silica, alumina, kaolin, morierite, cordierite, zirconia minerals and the like; any of the monomeric and monomer/polymer species listed above mixed or covalently bound with minerals such as silica, alumina, kaolin, morierite, cordierite, zirconia minerals and the like; proteins bound to silica, titania, and the like; silicon-containing polymers; and polyhydroxyalkanoic acid:salt complexes. Such particles, when used in toothpaste, may act as an abrasive material, and thus may supplement, or perhaps even replace, the abrasive materials commonly used in toothpastes.

The more preferred degradable materials are polymers such as polyglycolic acid, polylactic acid, and copolymers of glycolic acid and lactic acid, and esters of glycerol. These polymers are well-known and commercially available. For example, polyglycolic acid is available from the American Cyanamid Company (Dexon®) and Polysciences, Inc.; polylactic acid is available from Polysciences, Inc.; and copolymers of glycolic acid and lactic acid are available from American Cyanamid Company (Vicryl®), Ethicon, Inc. (Polyglactin 910) and Polysciences. Alternatively, the polymers can be synthesized according to known procedures. For example, polyglycolic acid can be prepared employing the ring opening polymerization of the dimeric ester of glycolic acid; polylactic acid can be prepared employing the ring opening polymerization of the dimeric ester of lactic acid; and copolymers of glycolic acid and lactic acid can be prepared employing the ring opening polymerization of the corresponding dimeric esters.

Other preferred degradable polymeric materials are commercially available and/or may be prepared by known procedures.



The particles optionally include a thin, non-porous, water-stable coating that prevents the particle from degrading or swelling when the particle is stored or incorporated into aqueous systems. Preferred coating materials include poly(methyl methacrylate), polystyrene, beeswax, carnauba wax, petroleum wax, polyhydroxylalkanoic acid, glycolipids, glycerides, phospholipids, and glycerol distearate. The coating materials may be materials (like polystyrene, waxes, or poly(methyl methacrylate) that do not degrade when exposed to enzymes in the mouth, or may be materials (like glycerol distearate, polyhydroxyalkanoic acid, and glycerides) that do degrade when exposed to enzymes in the mouth. All of these materials are commercially available. Preferably the coating constitutes no more than about 10% of the particle diameter.

In alternative embodiments, the particles are composed entirely of the degradable material. The degradable material may be a non-water stable material, or may be a material like glycerol distearate that is water stable but degrades when exposed to mouth enzymes.

The preferred particles can be made by numerous conventional, well-known methods. These include solvent evaporation methods, with or without a surface active agent as necessary, coacervation in all its various forms, pan coating, air-suspension coating, press coating, spray-drying, rotational suspension-separation techniques, melt coating methods, interfacial polymerization, melt-granulation processes and any and all related methods that yield the desired particles as described. Such methods may or may not use organic solvents. Such methods may encapsulate from solution, from the melt or in powdered (solid state) form. Once formed, the particles may be chemically modified (e.g., charged or made magnetic). The

particles are then coated with a water stable material. See, for example, the particle-making and particle-coating procedures described generally in Parrott, Pharmaceutical Technology, pp. 86-91 (Burgess Pub. Co. 1970); Deasy, 5 Microencapsulation and Related Drug Procedures, pp. 1-60 (Marcel Dekker, Inc. 1984); Muller et al., J. Controlled Release, 20 (1992):237-246; Pekarek et al., Nature, v. 367 (1994):258-60; Muller et al., Pharm. Pharmacol. Lett. v. 3 (1993):67-70; and Juliano (ed.), Drug Delivery Systems 10 (Oxford University Press 1980).

To desensitize a hypersensitive tooth, the tooth surface initially is polished. The preferred particles then are applied to the polished surface. Application can take numerous forms. For example, the particles may be applied 15 in the form of an aqueous dispersion that includes, e.g., between 0.01% and 5% particles by weight, that is agitated against the tooth surface for 1-5 minutes. Alternatively, the surface is exposed to a pressurized jet of the aqueous dispersion e.g., at a pressure of about 30 psi for about 20 20 seconds, or the surface is brushed with bristles that are saturated with particles, for 1-3 minutes. Each of these procedures, when performed on a tooth that had been removed from the mouth, is effective at blocking the exposed tubules in the dentin of the tooth with the particles.

25 FIGS. 1a, 1b, 2a and 2b show the dentin surface before (1a and 1b) and after (2a and 2b) a 5 minute exposure to a 0.5% (by weight) aqueous dispersion of poly(lactide-co-glycolide) ("PLGA") particles. Prior to exposure to the dispersion, the exposed tubules in the dentin are empty; 30 after exposure they are substantially filled with the particles present in the dispersion. (FIGS. 1a and 2a were both taken at 800x magnifications, and FIGS. 1b and 2b were both taken at 4000x magnifications).

An alternative procedure for applying the particles to the tooth is to soak a cotton pellet with an aqueous dispersion of the particles, and then rub the cotton pellet for 1-3 minutes over the polished surface of the tooth.

5 The PLGA particles used in the above example were prepared according to the following procedure:

1. 100 mg of PLGA (80:20) were dissolved in 5 mL of methylene chloride.

2. 100 mL of a 0.10% polyvinyl alcohol (PVA) solution in water was prepared. The polyvinyl alcohol was 10 13,000-23,000 MW and was 87-89% hydrolyzed.

3. The PVA solution was stirred with a Tekmar high speed mechanical stirrer (24,000/min).

4. The PLGA solution was added all at once to the 15 PVA solution. This solution was stirred in a fume hood for 20 min. to drive off the methylene chloride.

5. The resulting suspension was centrifuged. The particles were washed with distilled water. Micrographs showed that a polydisperse particle size distribution 20 resulted (0.1-1  $\mu\text{m}$ ) and that the particles were irregular in shape.

Other embodiments are within the claims. For example, the particles can be included in a dentifrice (toothpaste) or a mouthwash; when the dentifrice or 25 mouthwash contacts the surface of a tooth the particles will fill in the tubules. This approach can be used, in particular, to replenish particles that were previously blocking a tubule but have, to some extent, washed out of the tubule or degraded over time. If a mouthwash is used, 30 it may be applied under pressure, using any commercially available water-jet appliance (e.g., a Braun MO 5000). The particles can also be applied, for example, by including them on the bristles of toothbrushes or on dental floss.

While the times, pressures and other conditions given above were preferred in a laboratory setting or home use, these conditions may be varied as desired to adapt them to a clinical setting, provided the time, pressure etc., is adequate to block the tubules. Effective conditions may be readily determined by those skilled in the art, e.g. by determining whether a patient's tooth is still sensitive after the treatment.

The filling of dentin tubules with the particles can be enhanced by using particles with a charged outer surface, or by using a swellable material like polyvinyl alcohol in the particles. When the particles include a swellable material, the particles preferably comprise a water-stable exterior. Significantly, a coated particle including a swellable material may be sufficiently small to flow readily into the tubules. But during application part or all of the coating deteriorates allowing water to contact the swellable material. As this material swells the particles become more tightly lodged in the tubule.

In addition, the particles may have an antimicrobial, analgesic or other therapeutic substance adsorbed on their surface or dispersed throughout the interior. These particles provide both the desensitization benefit of this invention, and an anti-microbial benefit or other benefit provided by the therapeutic agent selected. Examples of preferred antimicrobial agents, and how they may be incorporated throughout the particles, are described in U.S.S.N. 08/322,926, filed October 13, 1994.

Thus particles having essentially the same composition, e.g., degradable material and anti-microbial agent, can serve two functions, particularly when the particles are sufficiently small to fit readily in normal sized dentin tubules. But the particles may serve only one

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function (release of anti-microbial agent) if the particles are too large to effectively clog dentin tubules. A composition, e.g., an oral rinse, may include particles that are small enough to serve both functions and particles

5 having the same composition that do not desensitize the tooth. To determine whether such an oral rinse (or other composition) contains particles having an average diameter within applicant's preferred (0.01 micron to 3 micron) or more preferred (0.2 micron to 0.6 micron) ranges, the

10 particle size distribution of all of the essentially identically composed particles in the composition initially is determined. If at least 5% of the particles have an average diameter of between 0.01 micron and 3 micron, or more preferably between 0.2 micron and 0.6 micron, the oral

15 rinse includes particles that have an average particle size within the applicant's preferred or more preferred range.

**The claims defining the invention are as follows:**

1. A method for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said method comprising contacting said exposed tubules with particles, comprising a degradable material, as hereinbefore defined, that are sufficiently small to block or clog said dentin tubules in an amount effective to desensitize said tooth.
2. The method of claim 1, wherein said particles have an average diameter of 0.01 micron to 3 microns.
3. The method of claim 2, wherein said particles have an average diameter of 0.2 micron to 0.6 micron.
4. The method of any one of claims 1 to 3, further comprising polishing said surface of said tooth prior to contacting said tooth with said particles.
5. The method of any one of claims 1 to 4, wherein said degradable material is selected from the group consisting of polyglycolic acid, polylactic acid, copolymers of glycolic acid and lactic acid and glycerol disterate or other esters of glycerol.
6. The method of any one of claims 1 to 5, wherein said particles have a water-stable exterior.
7. The method of claim 6, wherein said water-stable exterior is in the form of a non-porous coating comprising a water-stable material which does not significantly degrade when contacted with enzymes found in the mouth.
8. The method of claim 7, wherein said water-stable material is selected from the group consisting of poly(methyl methacrylate), polystyrene and waxes.
9. The method of claim 6, wherein said water-stable exterior is in the form of a non-porous coating which degrades when contacted with enzymes found in the mouth.
10. The method of claim 9, wherein said water-stable material comprises glycerol disterate.
11. The method of claim 5, wherein said degradable material is a material which is water-stable.
12. The use of particles comprising a degradable material, as hereinbefore defined, for the preparation of a formulation for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said particles being sufficiently small to block or clog said dentin tubules in said hypersensitive tooth.
13. The use of claim 12, wherein said particles have an average diameter of 0.01 micron to 3 microns.
14. The use of claim 13, wherein said particles have an average diameter of 0.2 micron to 0.6 micron.
15. The use of any one of claims 12 to 14, further comprising polishing said surface of said tooth prior to contacting said tooth with said particles.



16. The use of any one of claims 12 to 15, wherein said degradable material is selected from the group consisting of polyglycolic acid, polylactic acid, copolymers of glycolic acid and lactic acid and glycerol disterate or other esters of glycerol.

17. The use of any one of claims 12 to 16, wherein said particles have a water-  
5 stable exterior.

18. The use of claim 17, wherein said water-stable exterior is in the form of a non-porous coating comprising a water-stable material which does not significantly degrade when contacted with enzymes found in the mouth.

19. The use of claim 18, wherein said water-stable material is selected from the  
10 group consisting of poly(methyl methacrylate), polystyrene and waxes.

20. The use of claim 17, wherein said water-stable exterior is in the form of a non-porous coating which degrades when contacted with enzymes found in the mouth.

21. The use of claim 20, wherein said water-stable material comprises glycerol disterate.

15 22. The use of claim 16, wherein said degradable material is a material which is water-stable.

23. The use of particles for the preparation of a formulation for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, which particles are substantially as herein described with reference to the example.

20 24. Particles comprising a degradable material, as hereinbefore defined, when used for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, said particles being sufficiently small to block or clog said dentin tubules.

25 25. The particles of claim 24, having an average diameter of 0.01 micron to 3 microns.

26 26. The particles of claim 25, having an average diameter of 0.2 micron to 0.6 micron.

27. The particles of any one of claims 24 to 26, further comprising polishing said surface of said tooth prior to contacting said tooth with said particles.

28. The particles of any one of claims 24 to 27, wherein said degradable material  
30 is selected from the group consisting of polyglycolic acid, polylactic acid, copolymers of glycolic acid and lactic acid and glycerol disterate or other esters of glycerol.

29. The particles of any one of claims 24 to 28, wherein said particles have a water-stable exterior.

30. The particles of claim 29, wherein said water-stable exterior is in the form of  
35 a non-porous coating comprising a water-stable material which does not significantly degrade when contacted with enzymes found in the mouth.

31. The particles of claim 30, wherein said water-stable material is selected from the group consisting of poly(methyl methacrylate), polystyrene and waxes.

32. The particles of claim 29, wherein said water-stable exterior is in the form of a non-porous coating which degrades when contacted with enzymes found in the mouth.



33. The particles of claim 32, wherein said water-stable material comprises glycerol disterate.

34. The particles of claim 28, wherein said degradable material is a material which is water-stable.

5 35. Particles comprising a degradable material, as hereinbefore defined, when used for desensitizing a hypersensitive tooth in a patient, said tooth comprising exposed dentin tubules, which particles are substantially as herein described with reference to the example.

Dated 29 January, 1999  
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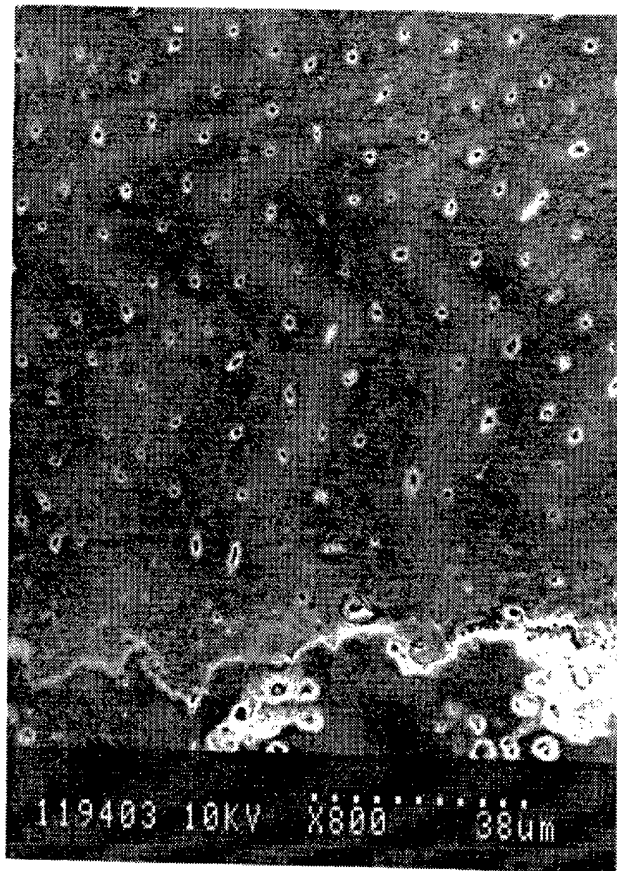


FIG. 1A

SUBSTITUTE SHEET (RULE 26)

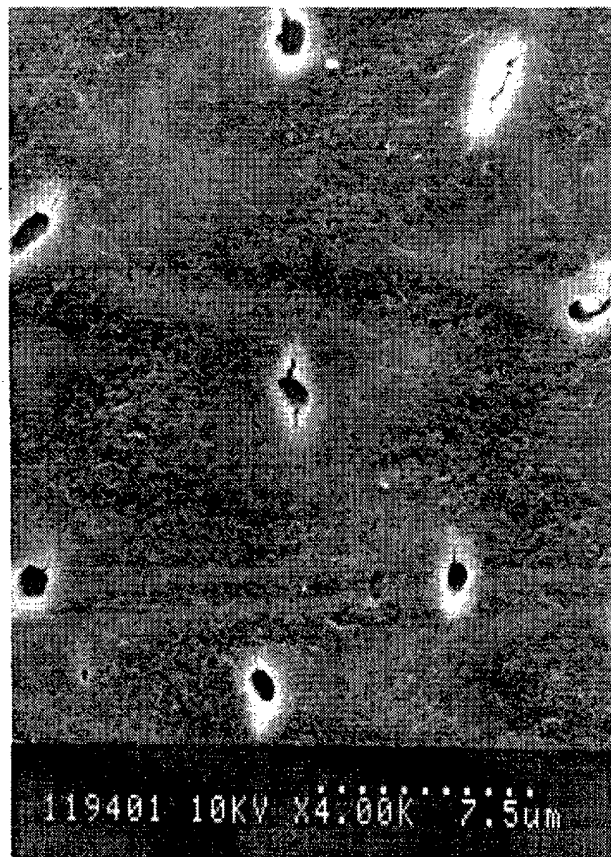


FIG. 1B

SUBSTITUTE SHEET (RULE 26)

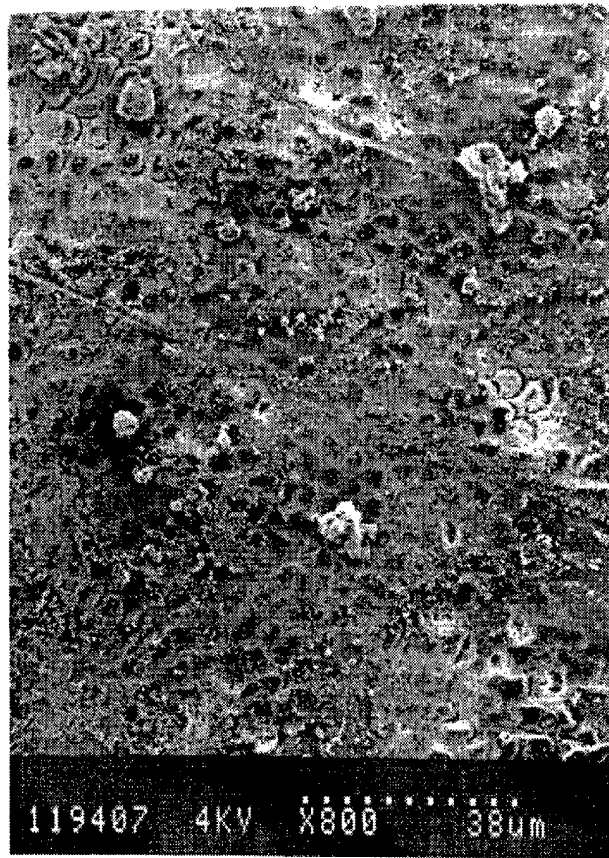


FIG. 2A

SUBSTITUTE SHEET (RULE 26)



FIG. 2B

SUBSTITUTE SHEET (RULE 26)