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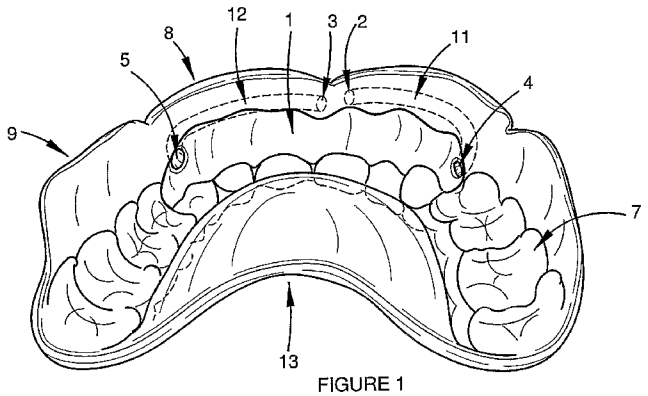

FIGURE 1

(57) Abstract: A bioactive delivery device for delivering a bioactive solution to the maxillary or mandibular dental, periodontal and/or mucosal tissues, a method of producing the delivery device and method of using the device are disclosed. The device includes a body, including a base (6), a buccolabial wall (8,9) and a lingual wall (30) shaped to conform to the dental, periodontal and/or mucosal tissues; a reservoir (1) formed in the base (6), buccolabial and/or lingual wall for holding a bioactive solution adjacent to a target site on the dental, periodontal and/or mucosal tissues (15). The reservoir (1) has an external inlet port (2) for receiving the bioactive solution and an external outlet port (3) for purging the reservoir, and a sealing means (21) to seal the bioactive solution within the reservoir (1). The inlet and outlet ports are in the closed until opened by connection with the respective supply and purging conduits.

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Bioactive delivery device

Field of the invention

The invention relates to the field of devices and therapeutics used in the treatment of conditions of the dental, periodontal and mucosal tissues. More particularly, the invention relates to methods of applying and localising bioactive solutions to the maxillary or mandibular teeth, periodontium or mucosa to maintain their activity while minimising the clearance, dilution and pH buffering effects of saliva.

Background of the invention

Bioactive treatments of the dental, periodontal and mucosal tissues all involve the localisation of the treatment agent at an effective concentration (activity) at the target site. Examples are: remineralisation - the localisation of the remineralising solution at the target site (eg the carious lesion) and diffusion of calcium, phosphate and fluoride ions into the carious lesion; bleaching – localisation of the bleaching agent at the extrinsic stain and or localisation and diffusion of the bleaching agent into the tooth for intrinsic stains; anti-tartar agents – localisation of the bioactive on the tartar to chelate and/or dissolve the solid calcium and phosphate phases; antimicrobials – localisation and diffusion into supragingival and subgingival dental plaque to access microbial pathogens; anti-inflammatories – localisation and diffusion of anti-inflammatory therapeutics into the gingival tissues; drug delivery – localisation and diffusion of any drug into the periodontal or mucosal tissues.

The problem with these localisation and diffusion related processes are that they require a concentration gradient to allow the bioactive to move to the target site. More important than the concentration of the bioactive is its chemical activity. With high chemical activity of the bioactive and an adequate exposure time efficacious results are achieved.

Intra orally there are a number of factors that limit this process. The mouth is a dynamic environment. Saliva is constantly secreted into the mouth and swallowed. Foodstuffs are entering the mouth and passing the tooth surfaces. Salivary proteins and bacteria

adhere to the teeth creating pellicle and dental plaques. Delivering a bioactive successfully to the target site in this environment is not an easy task.

Saliva regulates the pH of the intra oral environment. It has been shown that the ionisation of actives can limit their diffusivity (for example, neutral ions diffuse faster through charged membranes than charged ions). The level of ionisation of an active can be controlled by controlling the pH of the solution. Saliva contains numerous buffering systems that work to regulate the pH of the intra oral environment, therefore to maximise diffusion a means of controlling pH is necessary.

Additionally, a major impediment to bioactive delivery is that of salivary clearance. Salivary clearance is the effect of incoming fresh saliva together with swallowing reducing the concentration of exogenous substances (Edgar *et al*: British Dental Assoc. 2004). All the bioactive therapeutics mentioned above require substantial contact to allow the diffusion of the bioactive to the target site. To overcome the problem of salivary clearance numerous approaches have been taken. These approaches have normally involved changing the viscosity of the bioactive carrier or utilising a device to protect the bioactive. However, often this protection is limited.

Changing the viscosity of the bioactive carrier is a common approach. By adding glycerol or other thickeners to the bioactive carrier it has been possible to make the therapeutic agent stay on the tooth or gum surface for longer periods of time. This is often used in conjunction with a protective device such as a tray or strip. The problem with this approach is that by increasing the viscosity of the carrier the chemical activity of the bioactive decreases thereby decreasing its ability to diffuse to the target site. This greatly limits the effectiveness of the therapeutic.

Developing devices to protect the therapeutic has involved a great number of device designs. The most common of these is a custom made tray that is typically used for applying bleaching agents to the teeth. These devices commonly extend to the gingival margins and have reservoirs into which the bioactive (eg. viscous bleach agent) is expressed and applied onto the teeth for prolonged periods of time. Other devices that localise therapeutics have included strips of material deformed over the teeth,

microstructures protruding from the backing of the device to minimise the flow of medicaments away from the target site (Burgio US 6435873) and trays with greater extensions (Burgio US 6142780, Takeuchi and Hanada: J Oral Biosci 2005;47(3)243-252). However, none of these devices are specifically designed for the application of bioactive solutions to the teeth.

The problem with the currently described devices, particularly those frequently used, is that they do not provide good seals and allow some saliva to seep under the device to dilute and react with the bioactive or allow pellicle to form on the teeth. To keep the bioactive localised under the device the viscosity or hydrophobicity of the therapeutic agent is increased which decreases the chemical activity of the bioactive. This reduces the effectiveness of the bioactive compared to water based high chemical activity solutions. Additionally, currently available devices, either do not target specific tissues in the mouth or require a patient to be connected to a supply of solution for the treatment period.

Therefore, there is a need for a device which effectively delivers bioactive solutions to the target site, such as dental, periodontal or mucosal tissues, which overcomes the problems associated with salivary clearance and allows control over the pH and other chemical parameters. It is also desirable that the device be operable by the patient and allow the patient to perform normal tasks during the treatment period.

Summary of the invention

In a first aspect of the present invention, there is provided a bioactive delivery device for delivering a bioactive solution to the maxillary or mandibular dental, periodontal and/or mucosal tissues including:

a body, including

a base, a buccolabial wall and a lingual wall shaped to conform to the dental, periodontal and/or mucosal tissues

a reservoir formed in the base, buccolabial and/or lingual wall for holding a bioactive solution adjacent to a target site on the dental, periodontal and/or mucosal tissues;

an external inlet port in the body in communication with the reservoir for receiving the bioactive solution, the external inlet port being openable by connection to a supply of bioactive solution;

an external outlet port in the body in communication with the reservoir, the external outlet port being openable by connection to a conduit to purge the reservoir; and

a sealing means to seal the bioactive solution within the reservoir in contact with the target site.

The base, buccolabial wall and lingual wall preferably form a channel around the tooth structure. The buccolabial wall and/or lingual wall may extend into the mucosal sulcus (buccal of maxilla, buccal and lingual of mandibular) and posteriorly on the palate of the maxilla. Increased thickness and extension of the walls reduces the flow of saliva under the fitting surface due to the cohesive and adhesive properties of thin films of fluid. The body of the device includes a sealing means to seal the bioactive solution within the reservoir. The sealing means may be a sealing agent of any suitable viscous material, such as, but not limited to, methylvinylether or carboxymethylcellulose. Additionally, a seal may be achieved by inflating an air filled chamber that is contained in the device that surrounds the reservoir. The air filled chamber seal could be inflated by delivering a small volume of air via a syringe or compressed air or air pumping device. The sealing means is preferably located adjacent to the periphery of the reservoir. The sealing means improves the water or solution tightness of the reservoir and minimises the amount of saliva passing under the device and bioactive migrating away from the target site.

The inlet port and/or outlet port is preferably located in the buccolabial wall or base for easy access by the patient or dental practitioner. The inlet port and/or outlet port may

simply be the closed end of the conduits communicating with the at least one reservoir with the port opened by the insertion of a syringe into the closed end. Once the syringe needle in removed the material of the conduit closes around the insertion hole to close the port. In another form of the invention, the inlet and/or outlet port includes a valve having an open position and a closed position providing a direct conduit through a wall of the body to the reservoir. The valve may be adapted to receive a delivery tube which delivers the bioactive solution from an applicator, such as a syringe.

The valve is preferably pre-loaded such that the valve is normally in the closed position. Pre-loaded valves may include spring-loaded valves or duckbill valves (i.e resilient pivoting valve flaps which seal against each other). The use of pre-loaded valves in the closed positions enables the bioactive delivery tube to be simply inserted into the inlet to delivery the bioactive solution to the reservoir or purge saliva, and/or air from the reservoir. This is achieved without the need for closures to ensure the reservoir is sealed against the external environment.

The outlet port is preferably positioned superiorly to or above the inlet to enable the bioactive solution to be filled from the bottom, thereby enabling the air to be purged out the outlet port while avoiding entrapment of air bubbles.

The body preferably further includes a plurality of reservoirs, each reservoir position being adjacent to a target site for treatment with a bioactive solution. The reservoirs may be separate or interconnected with the positioning of each reservoir being selected to correspond to treatment of predetermined tissue.

The device of the present invention takes advantage of the higher chemical activity available in a solution of the bioactive ingredient. The device enables bioactive solutions of low viscosity to be applied thereby having high diffusion rates of the bioactive through the carrier medium of the bioactive solution.

The device localises bioactive material in solution to the teeth while protecting them from the oral environment. These bioactive solutions include but are not limited to: remineralising solutions; pre-treatment solutions for remineralisation or other

treatments; bleaching solutions; anti-tartar solutions; antimicrobial solutions; desensitising solutions; anti-inflammatory solutions and any other bioactive that can be applied in a solution.

The delivery system has the benefit of the bioactive solution displacing the saliva, water and air from the reservoir. The bioactive therefore avoids significant contact with the saliva and thus obviates saliva's pH buffering effect. The control of the bioactive solution's pH is of particular importance to control the ionisation of actives to enhance their diffusivity. The delivery system also allows modification of plaque or pellicle while it is protected from the oral environment prior to subsequent treatment with another bioactive solution.

The reservoir's seal maintains the bioactive solution in contact with the target site for sufficient time and with sufficient chemical activity to achieve efficient and effective treatment results.

The device effectively functions as a biochemical reactor, in which the treatment reaction taking place at, and/or proximal to the target site is optimised through controlling the kinetic and/or thermodynamic parameters such that the reaction rate and/or degree of reaction is controlled. This is achieved through isolating the target site from the internal chemical processes within the mouth and replacing them with a controlled chemical process favourable to the desired oral treatment.

To further promote the desirable chemical reactions in the oral treatment, the device may further include any chemical reaction parameter modifier which promotes the desired chemical reaction, such as temperature, motion or light modifiers. The modifiers may be powered by small batteries built into the device. An example of a temperature modifier could be a heating pad overlying the reservoir. An example of a motion modifier may be a sonicator that could increase the energy of the bioactive solution to promote diffusion. An example of a light modifier is an emitter of a certain frequency of light that could increase the activity of bleaching agents.

Importantly, the device is simple to use thus enabling the patient to perform treatments at home. Further, the device is comfortable to wear, thus promoting the likelihood of the patient wearing the device for the required period of time.

The described invention provides a highly protected environment that localises the bioactive ingredient in solution for prolonged time periods to allow maximal diffusion to the target site for improved therapeutic action.

In a second aspect of the present invention, there is provided a method for the treatment of dental, periodontal and/or mucosal tissues with a bioactive solution, the method including the steps of:

(1) fitting a bioactive delivery device to the dental, periodontal and/or mucosal tissues, the bioactive delivery device including:

a body, including

a base, a buccolabial wall and a lingual wall shaped to conform to the dental, periodontal and/or mucosal tissues; and

a reservoir formed in the base, buccolabial and/or lingual wall for holding a bioactive solution adjacent to a target site of the dental, periodontal and/or mucosal tissues; the body having an external inlet port in communication with the reservoir for receiving the bioactive solution and an external outlet port in communication with the reservoir, and

(2) connecting a supply of bioactive solution to the external inlet port and a conduit to the external outlet port to open the respective inlet and outlet ports;

(3) delivering the bioactive solution through the inlet port to the reservoir adjacent the target site and purging the reservoir through the external outlet port, and

(4) closing the inlet port and outlet port of the reservoir to maintain the bioactive solution within the reservoir.

The inlet port is preferably automatically closed by removing the supply of bioactive solution and the outlet port is closed automatically once the purge conduit is removed. The method may further include the step of forming a seal between the reservoir and the patient's teeth and/or gum structure with a sealing means

In a preferred form of the invention, the rate of delivering the bioactive solution preferably results in laminar or plug flow of the bioactive solution within the reservoir. Plug flow of the bioactive solution ensures efficient displacement of contents of the reservoir (eg. saliva, water, air) without intermixing between the bioactive solution and the contents of the reservoir. The bioactive solution is therefore substantially free of contaminants which may detrimentally effect the oral treatment.

The turbulence of the delivery solution may be determined by use of the Reynolds number, which has the following equation:

$$Re = \frac{\rho v_s L}{\mu} = \frac{v_s L}{\nu} = \frac{\text{Inertial forces}}{\text{Viscous forces}}$$

where:

- v_s - mean fluid velocity,
- L - characteristic length (equal to diameter $2r$ if a cross-section is circular),
- μ - (absolute) dynamic fluid viscosity,
- v - kinematic fluid viscosity: v = μ / ρ,
- ρ - fluid density.

Laminar flow or plug flow occurs at low Reynolds numbers (eg. <2000), where viscous forces are dominant, and is characterized by smooth, constant fluid motion, while turbulent flow, on the other hand, occurs at high Reynolds numbers (e.g. > 4000) and is dominated by inertial forces, producing random eddies, vortices and other flow fluctuations.

If plug laminar or plug flow is not able to be provided, it would be desirable to introduce a purging solution into the inlet of the reservoir prior to introduction of the bioactive solution to wash saliva and displace air and water from the target site. The purging solution is removed through the outlet to the reservoir.

To ensure that the bioactive solution is delivered to the reservoir under plug flow conditions, the delivery step preferably further includes the step of attaching a delivery tube to the input and supplying bioactive solution through the delivery tube into the reservoir by an applicator, such as a syringe. The delivery tube preferably has a sufficiently small diameter to inhibit excessive flow rates of the bioactive solution such that plug flow is promoted.

The delivery step preferably delivers sufficient bioactive solution into the reservoir such that the bioactive solution fills substantially all of the reservoir.

The step of sealing the inlet and outlet of the reservoir may be automatic if the inlet and outlet include one way valves. Alternatively, the sealing step may include manually adjusting the inlet and/or outlet valve to the closed position, or sealing the inlet and/or outlet with a closure or sealing cap.

Bioactive agents in solution may have short shelf lives. If shelf life of a bioactive solution is problematic it could be provided as separate components eg. two separate liquids or a powder and liquid. At the time of delivery the components could be mixed and delivered into the reservoir. One example would be a powder and liquid system. The powder may contain the bioactive and the liquid may contain the water and acid or base. Immediately prior to delivery into the reservoir the two components would be mixed. One means would be via a mixing tip built into a two compartment syringe.

In a third aspect of the present invention, there is provided a method of producing a bioactive delivery device including the steps of:

making an impression of the dental, periodontal or mucosal tissues containing at least one target site;

creating a model from the impression;

modifying the model by applying a spacing material to the model corresponding to each target site such that the spacing material replicates at least one reservoir to be formed in the device;

producing the body of the device including a base, a buccolabial wall, a lingual wall, the at least one reservoir having a complementary configuration to the modified model and an external inlet port and external outlet port communicating with the at least one reservoir.

The body of the device may be formed or moulded by thermoforming a plastic blank onto the model, injection moulding, or any of the processes suitable to create a plastic body from the modified model.

The step of producing the body may further include the step of attaching a valve to the inlet port and/or outlet port. A delivery tube may be removably attached to the inlet valve and a purge conduit removably attached to the outlet port.

Alternatively, the delivery tube may be permanently attached to the inlet. To internalise the delivery tubing within the device, a further plastic blank may be thermoformed over the delivery tubing. In this particular embodiment, a valve may be attached to the feed end of the delivery tube, with the valve having the inlet port to receive an applicator, such as a syringe.

In a fourth aspect of the invention, there is provided a kit for forming a bioactive delivery device by the method described above including

model material to create a model from an impression of dental, periodontal or mucosal tissues containing at least one target site;

spacing material for modifying the model to create at least one reservoir corresponding to at least one target site;

thermoplastic material to form the body of the bioactive delivery device; and

conduit material to connect the at least one reservoir to external inlet and outlet ports in a wall of the formed bioactive delivery device.

Brief description of the drawings

Figure 1 is a perspective back view of a bioactive delivery device fitted to a patient's teeth in accordance to one embodiment of the present invention;

Figure 2 is another perspective front view of the bioactive delivery device of Figure 1;

Figure 3 is an enlarged side sectional view of the bioactive delivery device of Figure 1;

Figure 4 is a photograph of the material required to produce a bioactive delivery device in accordance to one embodiment of the present invention, the materials including (1) a special tray with polyvinylsiloxane impression with sulci extension; (2) primary stone model; (3) Duplicate of model shown in (2) with wax reservoir space and trimmed ready for a plastic blank to be thermoformed onto it; (4) 2 x 2mm thick Erkoflex blanks; (5) 1mm diameter plastic tubing with wire to keep tube patent (clear); and (6) Syringe and needle to insert liquid into device;

Figure 5 is a photograph of stone models produced in the production of bioactive delivery devices of the present invention;

Figure 6 is a series of photographs of a bioactive delivery device of the present invention at various stages of its production;

Figure 7 is a series of intra oral photographs of the bioactive delivery device being fitted to a patient;

Figure 8 is a series of intra oral photographs depicting the sealability of the bioactive delivery device of the present invention; and

Figure 9 is a perspective view of an embodiment of the invention with a heating element for the reservoir.

Detailed description of the embodiments

As illustrated in Figures 1 to 3, in a preferred embodiment of the present invention, the bioactive delivery device includes a body having a base 6,a buccolabial wall including a buccal sulcular extension 9 and an anterior sulcular extension 8. The base 6, the buccolabial wall 8, 9 and a lingual wall 30 define a channel 35 that is generally complemental in configuration to the patient's tooth structure 15. The buccolabial and lingual walls preferably extends at least in part along the gingival margin 16 of the tooth structure 15. The gingival extension may vary from an extension to sulcular reflection 20 with frenal relief 10 to a smaller extension of at least 2 mm past the gingival margin 16 to allow sufficient sealing agent 21 to be applied to the device. As illustrated in Figure 3, the bioactive delivery device fits securely over the patient's tooth 15, with buccolabial wall 8 extending adjacent to the lip 14 to the reflection of the sulcus 20. The palatal wall extends past the gingiva 16 and adjacent to the palatal mucosa.

The channel 35 includes a reservoir 1 for holding a bioactive solution adjacent to a target site of the tooth 15 or gum (i.e gingiva 16 and/or palatal mucosa 17) structure. The reservoir 1 has an inlet which includes an external port 2 which communicates with an internal opening 4 through a connecting inlet tube 11. The reservoir 1 also includes an outlet which includes an internal opening 5 which communicates with an external port 3 through a connecting outlet tube 12.

The internal inlet 4 and outlet 5 are preferably located at opposing ends of the reservoir to enable efficient displacement of the contents of the reservoir (eg. saliva, water, air) without intermixing between the bioactive solution and the contents of the reservoir. The internal outlet 5 is preferably positioned at or near the top of the reservoir to enable the gaseous content of the reservoir to be removed without excessive entrapment of the gaseous content within the bioactive solution.

The reservoir may extend to any target area 33 within the teeth, gum region which is covered by the bioactive delivery device. This may include a region adjacent to all of

the patient's teeth on the lingual side (i.e next to patient's tongue) and/or the buccolabial side (i.e next to the patient's lips or cheeks). Alternatively, or in addition to, the reservoir may be adjacent to a region of the gingiva 16 or palatal mucosa 17.

The bioactive delivery device may be in the form of a plastic tray of variable thickness custom made to fit over the patient's maxillary or mandibular teeth and gums. The bioactive delivery device of the present invention can be made from any plastic material such as but not limited to polypropylene, ethylene-vinyl acetate copolymer or polyethylene. The method of construction may be, but is not limited too, thermoforming, injection moulding or direct build up of plastic over the model.

The device can extend a variable distance into the mucosal sulcus (buccal of maxilla, buccal and lingual of mandibular) and posteriorly on the palate of the maxilla. The thickness and extension of the device reduces the flow of saliva under the fitting surface 7 due to the cohesive and adhesive properties of thin films of fluid. A sealing agent 21 may be used around the reservoir 1 prior to the device being seated in the mouth. The sealing agent 21 improves the water tightness of the device and prevents saliva from passing under the device and the bioactive solution from migrating away from the treatment area. The sealing agent 21 may be any viscous material such as but not limited to methylvinylether or carboxymethylcellulose.

Internally, the device contains at least one reservoir to contain the bioactive agent. Each reservoir may have a variable volume dictated by the volume of bioactive solution required for treatment. In some embodiments, it is preferable to have a large ratio of bioactive solution volume to target area to be treated. Each individual reservoir is accessed through access points or external ports 2,3. The access points or ports may include any valve or tube capping that prevents the egress of solution out of the reservoirs. Alternatively access ports 2,3 may be made of a resilient membrane which enables the inlet and outlet tubes to be opened by insertion of a rigid conduit and closes once the rigid conduit is withdrawn.

One access point or opening may allow the bioactive agent into the reservoir and the other access point or opening may allow air, water or saliva to be displaced. There can

be a variable number of reservoirs per device depending on the number of sites that require treatment. Eg – the anterior teeth may require one reservoir, whereas areas on the buccal of the lower molars bilaterally may require two individual reservoirs. These reservoirs can be at any site covered by the device to correspond to any site that requires treatment.

To allow the bioactive solution to be readily inserted into reservoirs of the device, the access points can be connected via tubing 11, 12 to a midline 40 positioned adjacent to anterior teeth. In one production method the buccolabial wall 8, 9 of the body includes a first layer 22 and a second layer 23, between which the tubin 11, 12 is secured.

Alternatively, the placement of an opening smaller than the diameter of screw valves can be drilled through the plastic buccolabial wall 8 into the reservoirs 1. Screw valves (not shown) may then be screwed into the plastic buccolabial wall of the device.

The tubing 11, 12 may be made from any plastic tubing or removable spacer placed in the device during construction to create a delivery space. In this way treating even the buccal surface of a wisdom tooth is possible as the access points are still in the midline. For multiple treatment sites the tubes may be coloured to correspond to different sites. The tubing preferably allows fluid flow in one direction only – either into or out of the device. In cases that involve the treatment of anterior teeth that are easily accessed, the reservoirs can be accessed directly by inserting a valve without tubing through the plastic of the device.

The bioactive solution may be contained and administered in any applicator that allows delivery into the reservoir 1. As the bioactive solution is delivered through one access point (inlet) any water, saliva or air would be displaced out the other access point (outlet).

In the case of carious lesions a pre-treatment phase may be conducted in the dental surgery. At home the patient applies the sealing means (eg. a sealing agent 21) around the edges of the reservoir, inserts the device and expresses or delivers the bioactive active into the reservoir(s). The device may be worn while the patient sleeps or around

the home during the day. After use the device is removed and cleaned with a tooth brush to remove any remaining sealing agent or other build ups. This process may be repeated until the desired result was achieved.

In order to promote the chemical reactions in the oral treatment, the device may include a chemical reaction parameter modifier which promotes the desired chemical reaction.

The chemical reaction parameter modifier may take the form of a heating element, light emitter or stirrer powered by a power source incorporated in the device or externally situated or pad overlying the reservoir, a sonicator that increases the energy of the bioactive solution to promote diffusion or a light emitter which emits a certain frequency of light to increase the activity of the bioactive agents. The modifier may be powered by a power source such as a battery incorporated into the device or the modifier may be connectible to an external power source.

Figure 9 is an embodiment of the invention illustrating this aspect of the invention including a heating element 84 overlying the reservoir. Wires 83 from the heating element 84, are provided to connect the heating element 84 to a battery 80 through battery contacts 81 and switch 82 for activating the heating element once the device is in place in the patient's mouth. The wires, battery, battery contacts and switch may all be contained within a moisture proof housing, enclosure or sleeve to electrically isolate the electrical circuit from the patient's mouth.

Remineralisation uses

Early carious lesions are characterised by a mineral rich surface layer and a mineral deficient subsurface. To improve the aesthetics and functional properties of a carious lesion new mineral needs to be formed in the subsurface lesion. To form new mineral a chemical activity gradient of calcium, and phosphate, with or without fluoride ions needs to be established. The larger the gradient the more ions will move into the subsurface lesion. Solutions containing calcium chloride, and sodium phosphate, with or without sodium fluoride at any pH either unstabilized or stabilized by any carrier or polymer are examples of bioactives that could be used to supply these ions.

If a remineralisation agent were directly applied to the tooth in solution they would quickly be cleared by saliva resulting in minimal net mineral gain in the lesion. If the ions were applied in a viscous form they would remain on the tooth longer but would have difficulty in diffusing into the tooth due to lower chemical activity and also a need to diffuse through the viscous medium as well. If applied in a viscous form under a device they would be somewhat protected from saliva but again have low chemical activity.

The described device and method allows a solution containing a high chemical activity of these ions to be placed onto the target area after saliva and other material has been purged from the target area with no or very minimal contact with saliva. This would allow prolonged exposure to ions which could diffuse into the lesion to form new mineral.

Bleaching uses

Dental bleaching is a popular dental service that improves the whiteness of teeth and removes staining. Side effects of this treatment are dental sensitivity and chemical insult to the soft tissues. Ill fitting trays and some bleach formations also lead to ingestion of the bleach. Bleaching products normally consist of molecules that slowly break down into hydrogen peroxide that can diffuse into the tooth to bleach stains. Given the effect of salivary clearance and dilution, these bleaches are often in viscous formulations to aid localisation and handling properties. More bleach is applied than required due to the loss of bleach by ingestion and deactivation by saliva. The high concentration bleaches can also burn the soft tissues if not contained adequately by the bleaching tray. The new device described provides a high quality seal localising a bioactive solution over the treatment area. It would allow a very precise amount of bleaching solution to be dispensed with a higher chemical activity than that of the viscous bleaches. This would reduce the chance of bleach being inadvertently ingested and provide a more efficacious result.

Anti-tartar uses

Tartar formation on teeth adjacent to salivary duct entrances in the mouth is a common problem that can hasten gum disease. Currently tartar removal is achieved by scaling or

root planing by a dental professional. The described device allows control over a target area. A device could be made as described below that would allow an anti-tartar formulation to bath selected teeth to dissolve tartar chemically. This would provide a high level of clean. Following a scale and clean unremoved crystals hasten the return of tartar as new crystals can nucleate off the remaining ones. A chemical clean in the described device following a mechanical clean would remove many of these remaining crystals and improve the cleanliness of teeth and slow the return of tartar. Chemicals that could be used as anti-tartar bioactive materials could include citric acid.

EXAMPLE 1

The following description is one set of materials used to construct a maxillary device for treating dental caries around the gingival margins of 6 upper anterior teeth.

Extensions

Plastic thickness – 2 to 4 mm

Gingival extension –maximum extension to sulcular reflection with frenal relief

Palatal extension – 2mm anterior to junction of the hard and soft palates

Reservoir extensions – 2mm deep covering gingival margins of teeth from right to left canines

Tube diameter – 1mm

Number of access points – 2 (inlet and outlet)

These dimensions are just one example of a range of many possible values.

Materials

The material used to form the tray (Figure 4) was 2mm thick Erkoflex ethyl-vinyl-acetate (Cat 581220, Erkodent, Western Australia, Australia) 44. The tubing 45 used was minimum volume extension tubing 180cm (Ref # 4097572, Braun, Australia) and the wire used to maintain tube potency was Wire-pak 0.71mm (0.71mm x 75 meters, Whites Wires Pty Ltd, Arndell Park, New South Wales, Australia). The sealer used in the prototype was Polident™ denture adhesive cream (GlaxoSmithKline, Ermington, New South Wales, Australia). The applicator 46 was a 6cc syringe with a 23 gauge needle. The indicator used in the sealing and location tests was blue food dye (blue food colour 133, Queen Fine Foods Pty Ltd, Queensland, Australia).

Construction method

An alginate impression is taken of the maxillary dental arch and poured up in stone. If the extensions of all sulci are recorded accurately then the device may be made off this model otherwise a special tray may be constructed and a secondary impression can be taken in a material such as alginate or polyvinyl siloxane 41 as illustrated in Figure 4.

A working model is fabricated in stone or plaster 42 . Wax is then applied to the stone model 42 to create the space required for the reservoirs in the target treatment sites. Figure 5A is a maxillary stone model 50. Figure 5B is a duplicate of model A with reservoir 53 created from wax covering teeth 13 to 23 at gingival margin (Dental caries type case). Figure 5C is a duplicate of model A with a reservoir 55 created from wax covering the full labial aspect of teeth from right to left canine (fluorosis or bleaching type case). The reservoirs were formed from wax having a thickness of between 1 to 2 mm. The model was duplicated and poured up in stone 43.

Instead of using wax to create the reservoir space, a fast set composite may be used to cover the affected areas and create the reservoir space. This would remove the need to duplicate the model.

Figure 6 illustrates the steps in the construction process. Figure 6A is a plastic blank 58 which is heat and pressure formed over the stone working model 53 with rough trim

of edges Figure 6B illustrates a reservoir access hole (inlet/outlet) 60, 61 drilled on a superior aspect of reservoir at the gingival margin of the canine. Figure 6C is an enlarged view of the reservoir access hole 60. Figure 6D shows plastic tubing 64 with wire bent 66 to shape of model. Figure 6E illustrates the plastic tube 64 and wire 66 inserted into reservoir 62 access hole 60 prior to be covered by a second thermoformed plastic blank. Figure 6F is an internal view of the bioactive delivery device, with reservoir space 62 extending from tooth 13 to 23. Figure 6G is a frontal view of device with tubing internalised, the device is trimmed with frenal relief. Figure 6H is an internal view with sealer 67 around reservoir. Figure 6I shows a syringe applicator 65 inserted into the inlet opening of the tubing 64.

The duplicated model is trimmed to the reflection of the sulci 43. Figure 6A illustrates a 2mm thick plastic blank 58 which was heated and thermoformed onto the model 53. The excess blank not sucked down over the arch was trimmed away. Two holes or openings 60 were drilled through a first buccolabial wall layer of the plastic blank 58 to allow access into the reservoir 62 (Figure 6B&C). These holes were positioned superiorly so that when the bioactive solution was inserted it filled from the bottom up with the remaining air travelling out to prevent trapping air bubbles.

To connect the reservoirs to the midline 1mm diameter plastic tubing 64 was cut to the desired length. A flexible wire 66 was threaded through the tube to ensure that the tube remained patent or open after the second blank was thermoformed over the tubing. The wire in the tube was bent to match the contour of the arch (Figure 6D). The tubing 64 was placed into the hole 60 in the plastic and stabilised by a small drop of sticky wax (Figure 6E). The second buccolabial wall layer (2mm thick) of the plastic blank was thermoformed over the device to internalise the tubing (Figure 6F). Using a fine bur the plastic covering the tube entrance was removed to expose a one way valve entry. The device was trimmed to follow 1 mm below the maximum curvature of the sulcus and the edges were polished. The wire 66 in the tubing 64 was then removed by pulling the wire through with thin nosed pliers to complete the device (Figure 6G&H). In an alternative embodiment, the valves and tubes can be positioned in a wax up of the device with sprues. A plaster key can be made and the wax can be boiled out. A heated thermoplastic material can then be injected into the flask to form the device.

The final intra oral step is the insertion of the completed bioactive delivery device 70. The device 70 was fitted and tested for comfort and fit. Any margins that were overextended were adjusted and polished. To educate the patient about the device the sealer 67 was dispensed into the device around the peripheral boundary of the reservoir 62 and the patient shown how to insert it. As shown in Figures 7A, 7B, 7C, the device 70 was then inserted and a coloured solution 72 is then injected by syringe 65 into valve 64 of the reservoirs to test the seal on the device (Figure 7B&C). Blue food dye was inserted into the prototype appliance and followed over a 2 hour time period. After 2 hours the blue food dye remained in the reservoir 62 as seen in Figure 8, which illustrates the device upon the reservoir being filled with the dye and after 30 minute intervals.

It will be appreciated that a number of alternative construction method may be used within the scope of the present invention. For instance, instead of using wax to create the reservoir space as in example one a fast set composite could be used to cover the affected areas and create the reservoir space. This would remove the need to duplicate the model.

Instead of running tubes to the midline holes thinner than the diameter of the screw valves can be drilled through the plastic into the reservoirs. Screw valves may then be screwed into the plastic of the device.

The valves and tubes may be positioned in a wax up of the device with sprues. A plaster key can be made and the wax can be boiled out. A heated thermoplastic material can then be injected into the flask to form the device.

Retention of bioactive solutions

The device made from the model shown in Figure 5C was used intra orally to test the efficacy of the bioactive delivery device to maintaining bioactive solutions against the target tissues. Two bioactive solutions were made, one containing 220 ppm sodium fluoride (NaF) and the other a 1% (w/v) solution of casein phosphopeptide stabilised amorphous calcium fluoride phosphate (1% CPP-ACFP). These solutions and the

subjects' unstimulated saliva were analysed to determine the concentration of sodium, potassium, calcium, fluoride, chloride and phosphate using ion chromatography (Dionex with CS12 and AS18 columns, USA). These solutions were delivered into the bioactive delivery device and after 30 or 120 minutes, removed and the concentration of ions remaining in the bioactive solution analysed. During use of the bioactive delivery device with a bioactive solution, saliva was collected and analysed to determine if there was leakage of ions from the device.

The results are shown Table 1. Following 30 minutes or 2 hour use of the bioactive delivery device containing 220 ppm NaF, 94% or greater of the fluoride remained in the reservoir against the target tissues. The saliva collected while the subject was wearing the bioactive delivery device containing a 220 ppm NaF solution was similar in composition to the initial saliva sample indicating that the device was not leaking. The calcium, phosphate and fluoride retention after 2 hours of exposure to the 1% CPP-ACFP solution in the bioactive delivery device was 87% or greater for these three ions. These results provide evidence for the high quality seal and ability of this device to localise bioactive solutions to the target tissues.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

It will also be understood that the term "comprises" (or its grammatical variants) as used in this specification is equivalent to the term "includes" and should not be taken as excluding the presence of other elements or features.

Table 1: Localisation of bioactive solutions in the bioactive delivery device

Solution	Time (min)	Na^+ (mM)	K^+ (mM)	Ca^{2+} (mM)	F^- (mM)	Cl^- (mM)	PO_4^{3-} (mM)
Unstimulated saliva	Initial	2.25 ± 0.09	28.88 ± 0.82	1.85 ± 0.09	0.07 ± 0.01	16.00 ± 1.92	9.24 ± 2.22
220ppm NaF	Initial	12.45 ± 0.24	0.07 ± 0.03	0.18 ± 0.12	10.60 ± 0.05	0.03 ± 0.00	0.52 ± 0.17
1% CPP-ACFP	Initial	11.23	0.44	41.76	5.26	1.04	21.91
220ppm NaF	30	20.55 ± 0.75	0.41 ± 0.10	4.51 ± 0.58	10.66 ± 0.08[a]	0.77 ± 0.13	0.15 ± 0.03
220ppm NaF	120	44.94 ± 0.04	1.30 ± 1.12	18.22 ± 0.30	9.95 ± 0.94[b]	2.75 ± 2.16	0.16 ± 0.03
1% CPP-ACFP	120	37.31	0.86	43.30[c]	5.00[d]	3.51	19.07[e]
Saliva during 220ppm NaF	120	2.00 ± 0.20	33.94 ± 3.10	1.72 ± 0.06	0.05 ± 0.01	15.85 ± 1.59	10.33 ± 0.77

[a] percentage fluoride retention = 101%

[b] percentage fluoride retention = 94%

[c] percentage calcium retention = 104%

[d] percentage fluoride retention = 95%

[e] percentage phosphate retention = 87%

CLAIMS

1. A bioactive delivery device for delivering a bioactive solution to the dental, periodontal and/or mucosal tissues including:

a body, including

a base, a buccolabial wall and a lingual wall shaped to conform to the dental, periodontal and/or mucosal tissues

a reservoir formed in the base, buccolabial and/or lingual wall for holding a bioactive solution adjacent to a target site on the dental, periodontal and/or mucosal tissues;

an external inlet port in the body in communication with the reservoir for receiving the bioactive solution, the external inlet port being openable by connection to a supply of bioactive solution;

an external outlet port in the body in communication with the reservoir for receiving the bioactive solution, the external outlet port being openable by connection to a conduit to purge the reservoir; and

a sealing means to seal the bioactive solution within the reservoir in contact with the target site.

2. The bioactive delivery device of claim 1 further including a chemical reaction parameter modifier to promote reaction of the bioactive solution in the reservoir with the target dental, periodontal and/or mucosal tissues.

3. The bioactive delivery device of claim 1 wherein the base, buccolabial wall and lingual wall form a channel around the dental, periodontal and/or mucosal tissues

4. The bioactive delivery device of claim 1 wherein the sealing means is a sealing agent.

5. The bioactive device of claim 1 wherein the sealing means is an inflatable chamber contained in the device surrounding the reservoir.

6. The bioactive delivery device of claim 5 wherein the inflatable chamber is located adjacent to the periphery of the reservoir.

7. The bioactive delivery device of claim 1 wherein at least one of the inlet or outlet includes a valve having an open position and a closed position providing a direct conduit through a wall of the body to the reservoir.

8. The bioactive delivery device of claim 7 wherein the valve is adapted to receive a delivery tube which delivers the bioactive solution from an applicator.

9. The bioactive delivery device of claim 7 wherein valve is preloaded in the closed position.

10. The bioactive delivery device of claim 1 wherein the outlet is positioned so that in use it is above the inlet to the reservoir.

11. The bioactive delivery device of claim 1 wherein the body includes a plurality of reservoirs, each reservoir position being adjacent to a target site for treatment with a bioactive solution.

12. The bioactive delivery device of claim11 wherein the reservoirs are separate.

13. The bioactive delivery device of claim 11 wherein the reservoirs are interconnected.

14. A method for the treatment of dental, periodontal and/or mucosal tissues with a bioactive solution, the method including the steps of:

(1) fitting a bioactive delivery device to the dental, periodontal and/or mucosal tissues, the bioactive delivery device including:

a body, including

a base, a buccolabial wall and a lingual wall shaped to conform to the dental, periodontal and/or mucosal tissues; and

a reservoir formed in the base, buccolabial and/or lingual wall for holding a bioactive solution adjacent to a target site of the dental, periodontal and/or mucosal tissues; the body having an external inlet port in communication with the reservoir for receiving the bioactive solution and an external outlet port in communication with the reservoir for purging the reservoir;

(2) connecting a supply of bioactive solution to the external inlet port and a conduit to the external outlet port to open the respective inlet and outlet ports;

(3) delivering the bioactive solution through the inlet port to the reservoir adjacent the target site and purging the reservoir through the external outlet port, and

(4) closing the inlet and outlet of the reservoir to maintain the bioactive solution within the reservoir.

15. The method of claim 14 further including the step of forming a seal between the reservoir and the patient's teeth and/or gum structure with a sealing means.

16. The method of claim 14 wherein the delivery of the bioactive solution to the device produces laminar or plug flow of the bioactive solution within the reservoir.

17. The method of claim 14 further including the step of introducing a purging solution into the inlet of the reservoir prior to introduction of the bioactive solution.

18. The method of claim 16 further includes the step of attaching a delivery tube to the input and supplying bioactive solution through the delivery tube into the reservoir by an applicator.

19. A method of producing a bioactive delivery device including the steps of:

making an impression of the dental, periodontal or mucosal tissues containing at least one target site;

creating a model from the impression;

modifying the model by applying a spacing material to the model corresponding to each target site such that the spacing material replicates each reservoir to be formed in the device;

producing the body of the device including a base, a buccolabial wall and a lingual wall a reservoir having a complementary configuration to the modified model and an external inlet port and external outlet port in communicating with the reservoir.

20. The method of claim 19 wherein the device is produced by a process selected from the group consisting of thermoforming a plastic blank onto the modified model, injection moulding, or a process suitable to create a plastic body from the modified model.

21. The method of claim 19 wherein the step of producing the body further includes the step of attaching a valve to the inlet and/or outlet.

22. A kit for forming a bioactive delivery device by the method of claim 19 including

model material to create a model from an impression of dental, periodontal or mucosal tissues containing at least one target site;

spacing material for modifying the model to create at least one reservoir corresponding to the at least one target site;

thermoplastic material to form the body of the bioactive delivery device; and

conduit material to connect the at least one reservoir to external inlet and outlet ports in a wall of the formed bioactive delivery device.

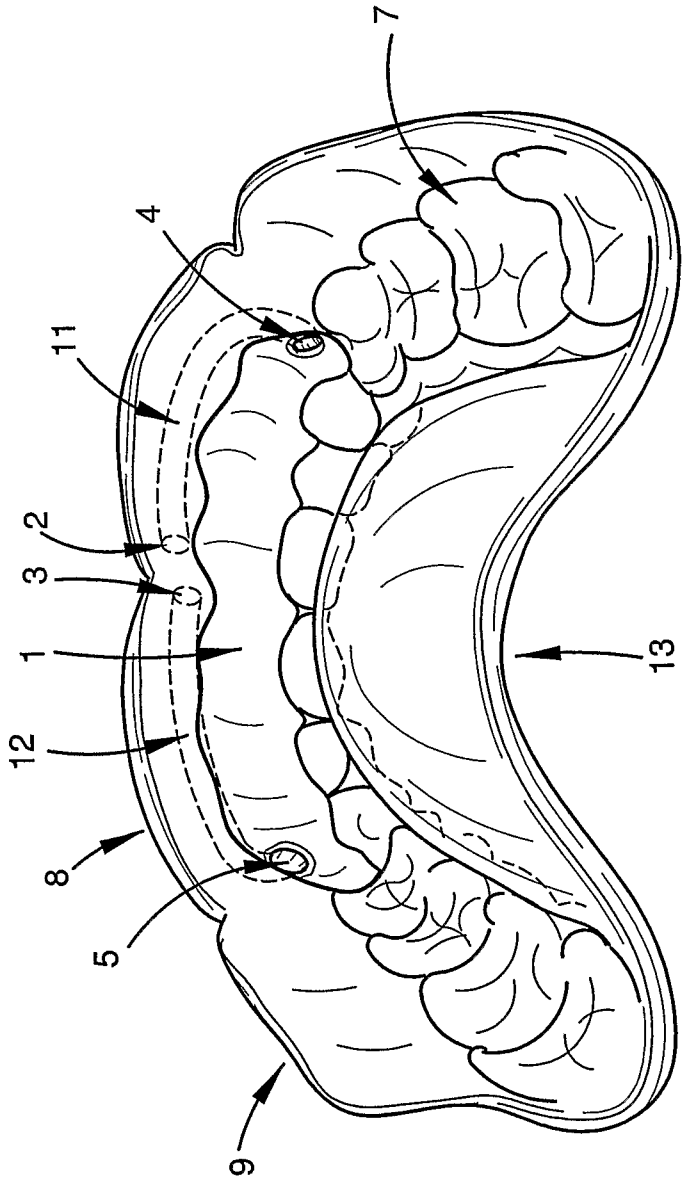

FIGURE 1

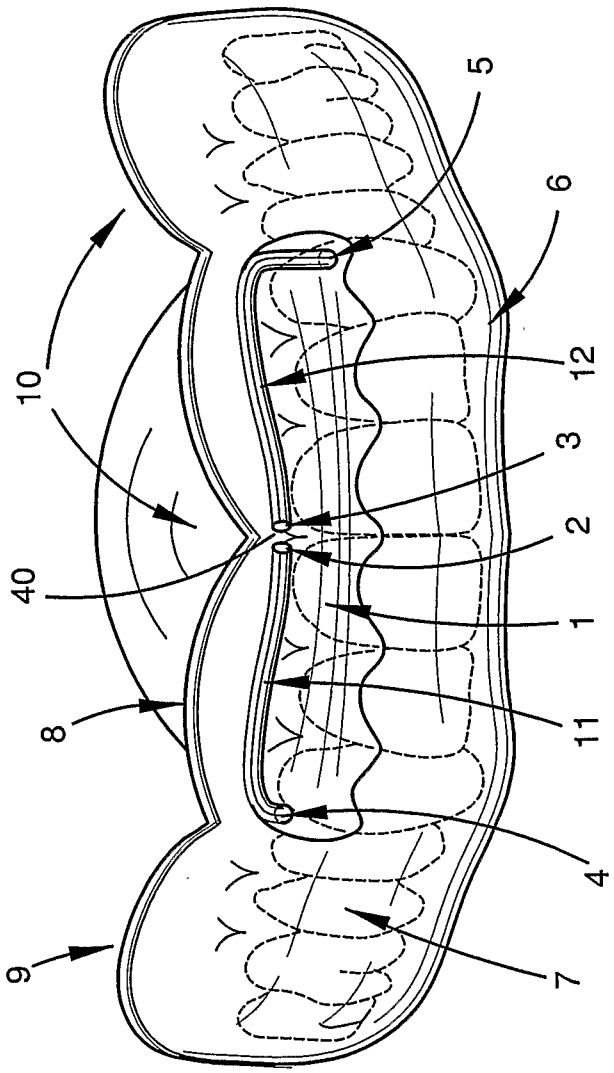

FIGURE 2

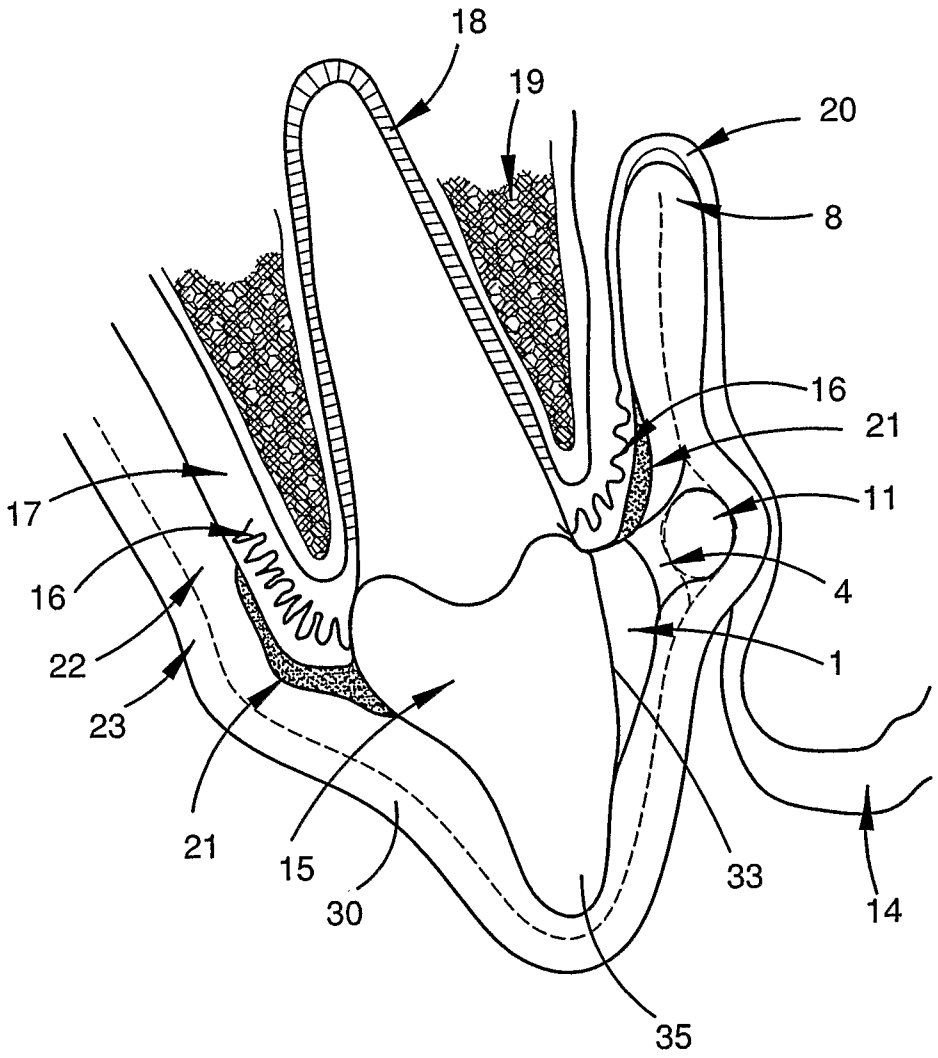

FIGURE 3

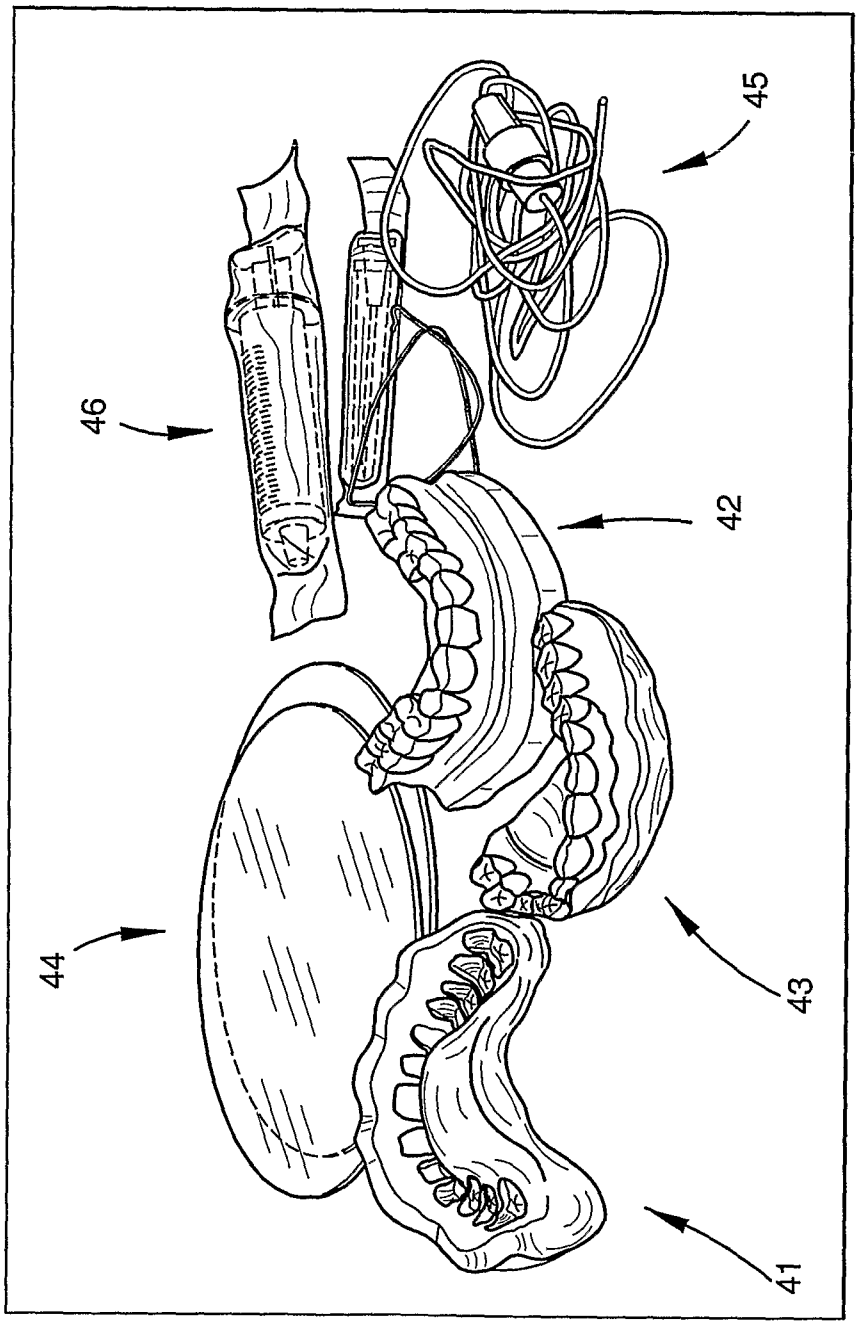

FIGURE 4

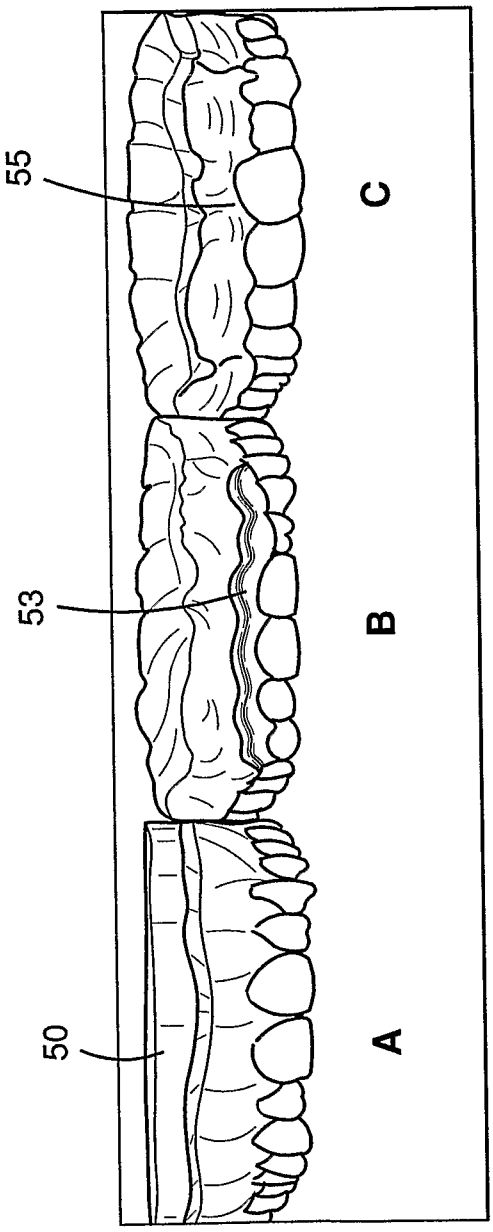

FIGURE 5

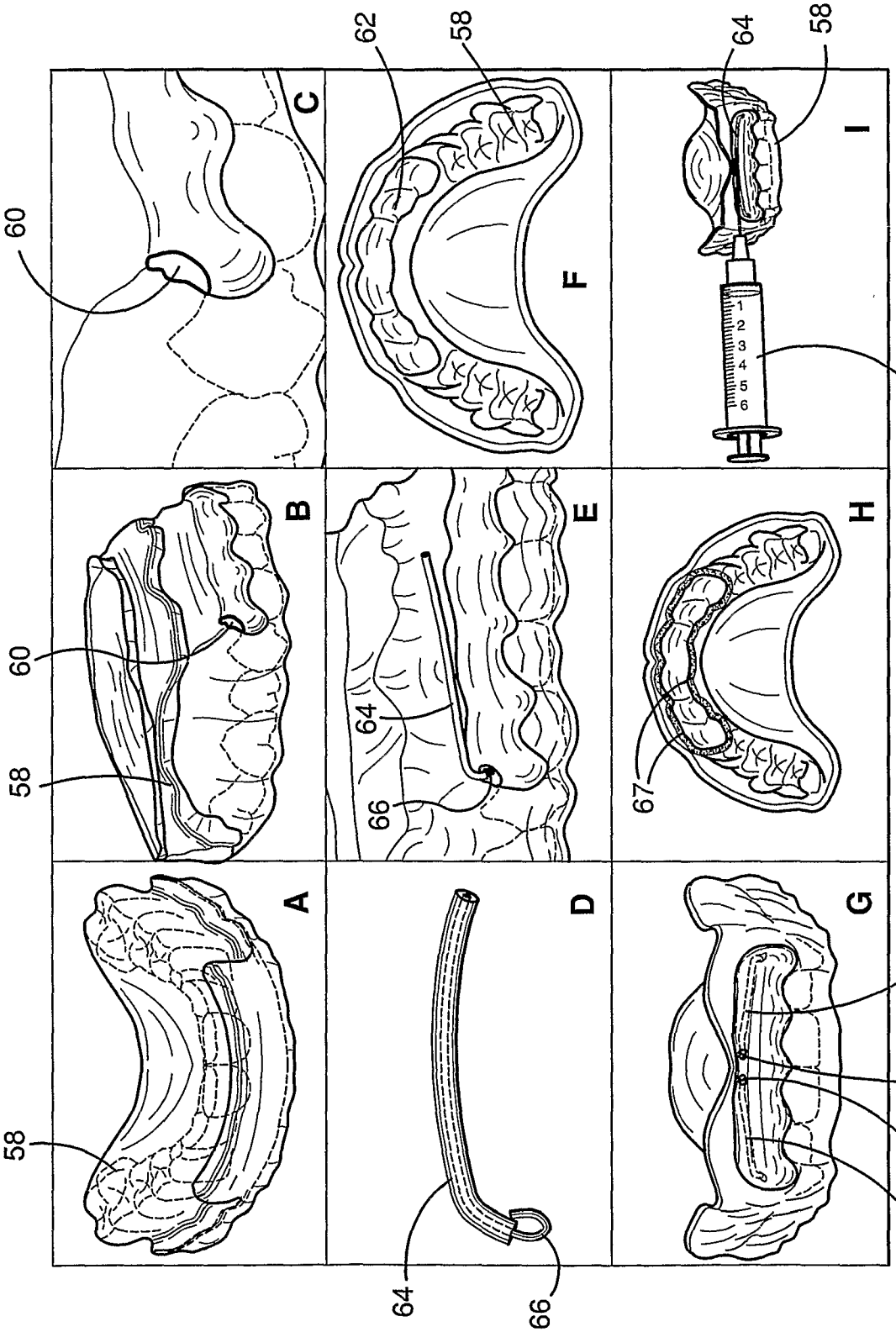

FIGURE 6

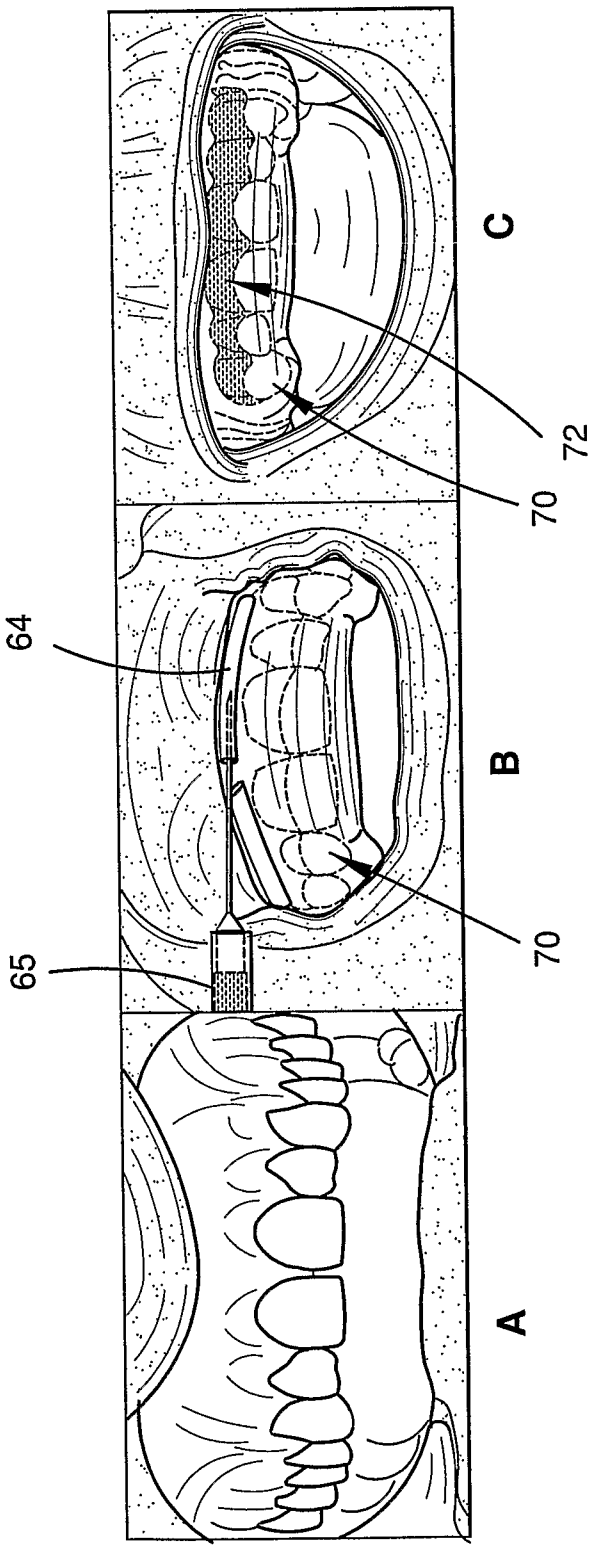

FIGURE 7

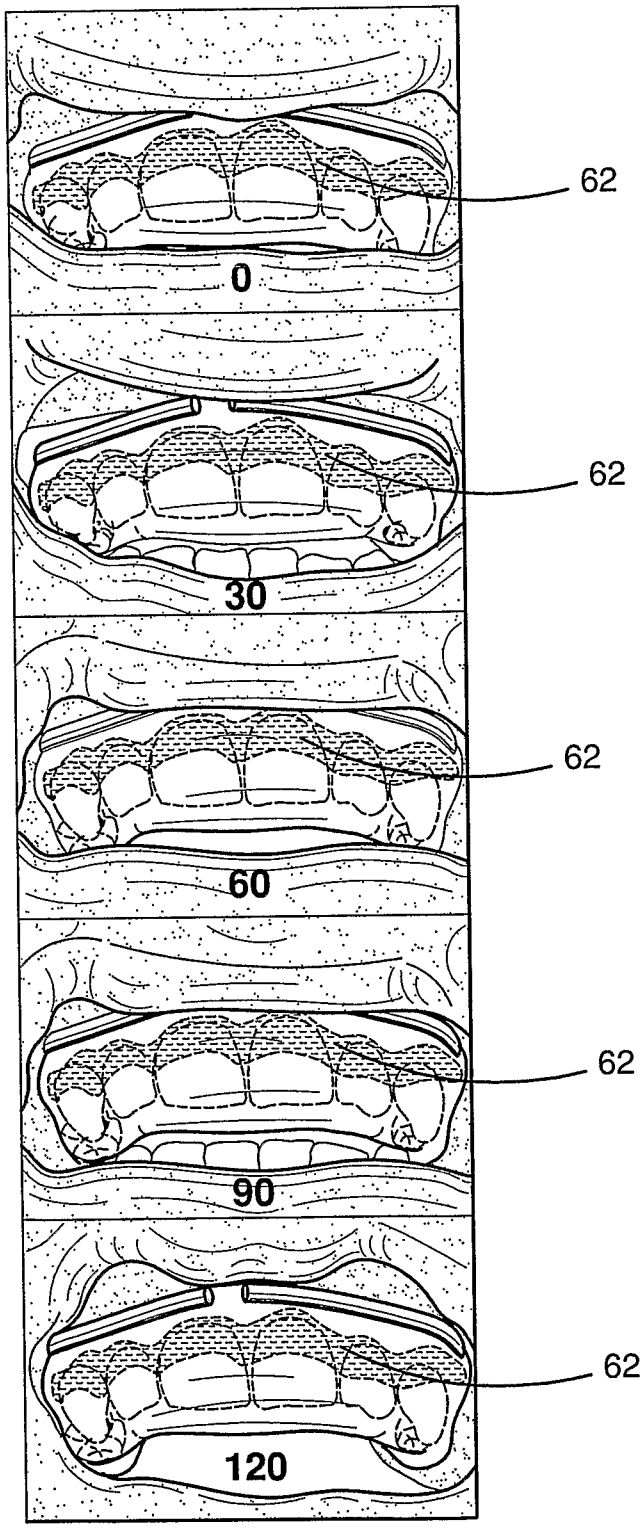

FIGURE 8

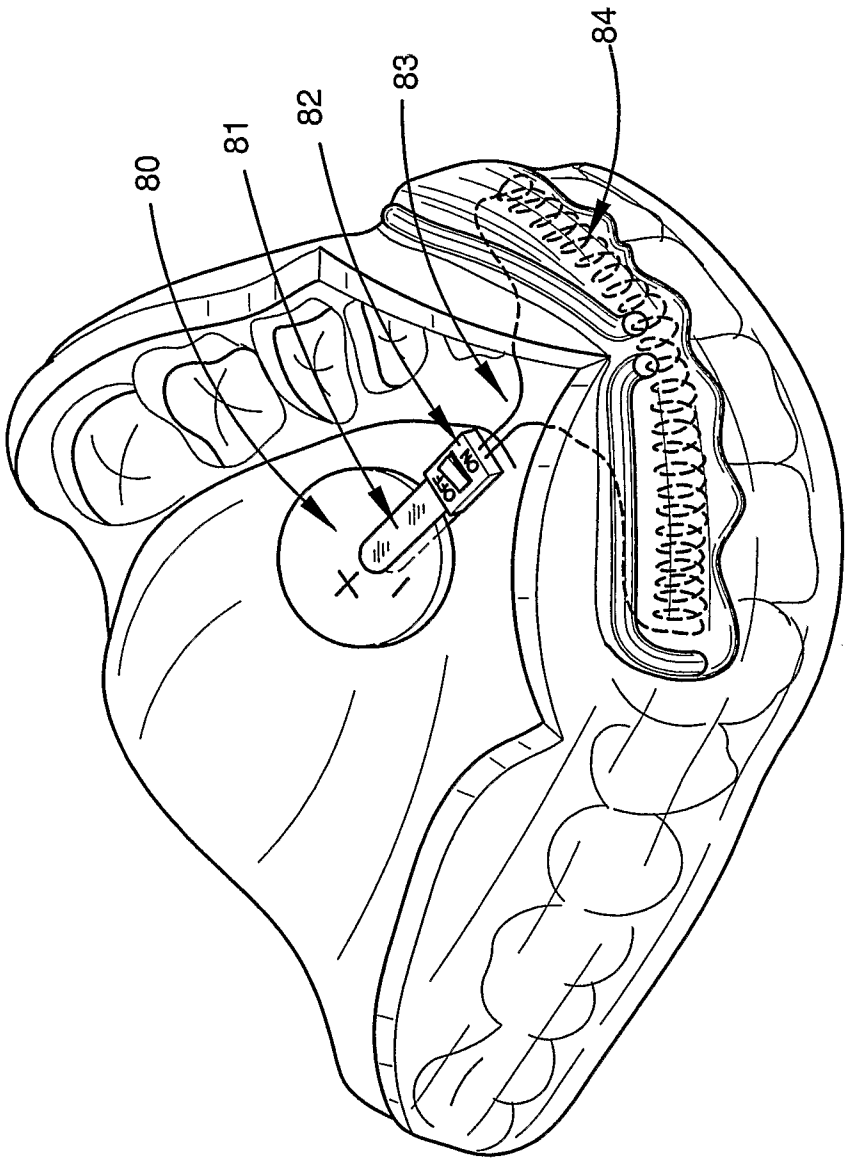

FIGURE 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000036

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. *A61C 5/02* (2006.01) *A61C 19/06* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
DWAPI, USPTO, EPO

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWAPI: A61C, A61M, medic+, drug, bioactive, pharmaceut+, agent, deliver+, releas+, dispens+, administ+, reservoir, chamber, container, vessel, receptacle, tooth, teeth, gum, gingiva+, modif+, chang+, promot+, alter+, enhanc+, improv+, increas+, control+, rate, +action, action

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3380446 A (MARTIN) 30 April 1968 Figures 1 to 5, abstract, column 3 lines 10 to 20	1 to 22
X	US 4560351 A (OSBORNE) 24 December 1985 Figures 1 to 3, column 3 line 48 to column 4 line 41	1, 3 to 22
X	US 3234942 A (SIMOR) 15 February 1966 Figures 6, 10 and 11, column 2 lines 54 to 57	1 to 13 and 19 to 22

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 February 2008	27 FEB 2008

Name and mailing address of the ISA/AU	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/000036

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/0012608 A1 (DARNELL) 9 August 2001 Figures 1 to 5, page 1 paragraph [0010] to [0012], page 3 paragraph [0029], page 10 paragraph [0077]	1 to 22
A	US 6142780 A (BURGIO) 7 November 2000 See whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/000036

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member							
US	3380446							
US	3234942							
US	4560351							
US	2001012608	US	6102705	US	6254391	US	6340301	
US	6142780	BR	9917016	EP	1148836	WO	0044303	

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX