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PATRICIA OCHOA SILVA
patricia.ochoa@ochoasilva.com

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Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional			
Vía PCT (Fase Nacional)	☒	Capítulo I	☒
No. Solicitud Internacional		PCT/ES08/000312	
Fecha de Presentación Internacional		6/Mayo/2008	

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 9 a 19	3/Noviembre/2010
modificada	Folios 79 a 158	3/Noviembre/2010
Reivindicaciones:	Folios 20 a 22	3/Noviembre/2010
modificada	Folios 42 a 44	3/Noviembre/2010

2. Objeto de la invención

Título de la solicitud: "COMPUESTO ACTIVADOR DEL MOVIMIENTO DENTARIO"

El problema planteado en esta solicitud consiste en la necesidad de suministrar una composición para disminuir la fricción o fuerza de rozamiento entre los alambres ortodóncicos y los brakets (Fl.30, pág.1).

Para resolver este problema técnico la solicitud en estudio proporciona una composición activadora según la reivindicación 1 (Fl.42, pág.12).

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 47/44; A61 Q 11/00.

3. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

Los usos de las reivindicaciones 1 a 7 no son patentables de acuerdo con los artículos aquí citados.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1, y sus dependientes aunque se encabezan con la expresión "una composición activadora del movimiento dentario" se refiere al uso de dicha formulación, ahora en ortodoncia (como se afirma en la descripción, Fl.34, pág.5). Sin embargo se advierte que en el Artículo *"Bioadhesive rheological, lubricant and other aspects of an oral gel formulation intended for the treatment of xerostomia"* se divulgan 20 composiciones, en forma de emulsiones para cuidado oral, que comprenden aceite de oliva (5 al 20%), Xilitol (5 a 15%), carbopol (0.5 a 1.5%), triclosan (0.1 a 0.3%), fluoruro de sodio (0.42%) y un antiinflamatorio como el triclosan (0.1 a 0.3%, tablas 1 y 2), que se utilizan para el tratamiento de xerostomia (síndrome de boca seca) en donde la presencia de ciertos excipientes altera las propiedades reológicas y que además con la inclusión de cantidades optimas de aceite vegetal, se logra una disminución en la fricción en la composición (abstract, Fl.59 y Fls.60 a 62). Por otro lado, el documento WO2007136586, divulga composiciones en forma de emulsiones (pág.19, línea 19), para el cuidado dental (pág.1, línea 16), que comprenden aceite vegetal como aceite de oliva (pág.14, líneas 24-26; pág.23, línea 23), antiséptico (pág.17, líneas 14-16, pág. 23, línea 13), polítrimetilen éter glicol (pág. 177, líneas 18 – 21), antibacterianos o fungicida (antimicrobianos, pág. 17, líneas 15 y 16), Fluoruro de sodio (pág.31, líneas 27 y 28), alantoina (pág. 16, línea 12).

Además, dado que no existe soporte en la descripción de una formulación (de las 6 preferidas) que defina cual es el aceite y el agente mezclador o estabilizante utilizados, la persona del oficio normalmente versada en la materia, tomando en cuenta el arte previo intercambiaría el carbopol de las composiciones de D1 por el polítrimetilen éter glicol, divulgado en las composiciones de D2, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual la invención sería obvia y no tendría nivel inventivo.

5. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque se reclama una composición y el título se refiere a un "compuesto activador", por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 y sus dependientes no son concisas porque los componentes se definen de forma genérica por su función, de manera que la reivindicación incluiría no sólo los compuestos actuales y que a futuro presenten la misma función; además

son infinitas las posibilidades de combinaciones dando lugar a infinitas composiciones. Además no existe soporte en la descripción de una formulación (de las 6 preferidas) que defina cual es el aceite y el agente mezclador o estabilizante utilizados.

Se requiere al Solicitante hacer las aclaraciones necesarias.

Descripción (Art 28 D 486)

La Descripción no divulga la invención de manera suficientemente completa para que la persona del oficio normalmente versada en la materia pueda ejecutarla ya que en los ejemplos de la composición (realizaciones preferentes, 1 a 6, Fls.38 y 39) en no se especifica el aceite y el agente mezclador o estabilizante utilizados para llevar a cabo, con éxito la invención.

Se requiere al Solicitante hacer las aclaraciones necesarias.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
06 NOV. 2012

Elaborado por: Lina del Carmen Mordecay Dunoyer
Revisado Por: Gloria Jacqueline Alfonso Roza
Aprobado por: José Luis Salazar López.

OK



Bioadhesive, rheological, lubricant and other aspects of an oral gel formulation intended for the treatment of xerostomia

H.M. Kelly^a, P.B. Deasy^{a,*}, M. Busquet^b, A.A. Torrance^b

^a School of Pharmacy, Trinity College, University of Dublin, Dublin, Ireland

^b Department of Mechanical and Manufacturing Engineering, Trinity College, University of Dublin, Dublin, Ireland

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Abstract

Xerostomia is commonly known as 'dry mouth' and is characterised by a reduction or loss in salivary production. A bioadhesive gel for its localised treatment was formulated to help enhance the residence time of the product, based on the polymer *Carbopol 974P*. The bioadhesion of various formulations was evaluated on different mucosal substrates, as simulations of the oral mucosa of xerostomic patients. Depending on the type of model substrate used, the mechanism of bioadhesion could alter. When the rheology of various formulations was examined, changes in bioadhesion were more easily interpreted, as the presence of other excipients caused an alteration in the rheological profile, with a change from a fully expanded and partially cross-linked system to an entangled system. Improving the lubricity of the product was considered important, with optimum incorporation of vegetable oil causing a desirable lowering of the observed friction of the product. The final complex formulation developed also contained salivary levels of electrolytes to help remineralisation of teeth, fluoride to prevent caries, zinc to enhance taste sensation, triclosan as the main anti-microbial/anti-inflammatory agent and non-cariogenic sweeteners with lemon flavour to increase the palatability of the product while stimulating any residual salivary function.

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Keywords: Xerostomia; Saliva substitute; Bioadhesion; Rheology; Lubricity; *Carbopol 974P*; Excipients

1. Introduction

Xerostomia is a condition characterised by a reduction or loss in salivary flow, often with a concurrent change in the composition of the saliva, resulting in dryness of the oral cavity. This leads to changes in oral pH and microflora, causing an increased risk of infection, dental caries, mucositis, gingivitis and periodontitis (Plankhurst et al., 1996). There is also an in-

creased risk of *Candida* infections and angular cheilitis (Chaushu et al., 2000). Xerostomia may lead to difficulties with some or all of the following, polydipsia, polyuria, sleeping, speaking, swallowing and mastication (Hamlet et al., 1997). There may be also changes in taste acuity (Mossman and Henkin, 1978).

There are a number of conditions that can result in the development of xerostomia. The most common are radiation treatment of the head and neck region, anti-cancer drug treatment and Sjögrens syndrome. However, other conditions have been reported to cause xerostomia including HIV (Schiodt et al., 1992), brain tumours and neurosurgical procedures (Ettinger, 1996).

* Corresponding author. Tel.: +353-1-6082784.

fax: +353-1-6082783.

E-mail address: pdeasy@tcd.ie (P.B. Deasy).

development of hopefully an improved product, which will be tested subsequently in a panel of xerostomia patients to confirm clinical efficacy.

2. Materials and methods

2.1. Materials

Calcium chloride, sodium chloride, zinc sulphate (Merck), *Carbopol 974P* (BF Goodrich), cottonseed oil, ethylenediaminetetraacetic acid (EDTA), phenylmethylsulphonylfluoride (PMSF), porcine gastric mucin (type II—crude), potassium chloride, potassium phosphate (monobasic), sodium azide, sodium fluoride, sodium lauryl sulphate (SLS), sorbitol (Sigma), lemon flavouring (Dragoco), magnesium chloride, triethanolamine (BDH), olive oil (Don Carlos), sunflower oil (Tesco), triclosan 5000 (Kumar Organic Products), xylitol (Lancaster) and water (glass distilled) were used. All reagents were GPR unless otherwise indicated.

2.2. Method for preparation of formulations

Various formulations, some of which are detailed in Tables 1 and 2, were prepared as outlined in the following method. The relevant quantities of sodium fluoride, calcium chloride, potassium chloride, sodium

chloride, magnesium chloride, potassium phosphate, zinc sulphate, xylitol, sorbitol and flavouring agent were added to 20 ml approximate of water and dissolved. The required quantity of *Carbopol 974P* was added with continuous stirring over 60 min and left overnight at room temperature to allow complete hydration of the polymer. In a separate beaker, SLS and triclosan were placed in 10 ml approximate of water, 1.0 ml of triethanolamine was added and the preparation was sonicated until the triclosan was fully solubilised. The solubilised triclosan solution was added to the hydrated polymer system, which was partially neutralised by the triethanolamine present in the triclosan solution. The pH was further adjusted to 6.75 ± 0.05 as a simulation of oral pH using triethanolamine and the product was adjusted to its final weight using water. If vegetable oil was present in the formulation, water was added to give the weight required before the addition of the oil. The oil was added and emulsification was carried out using an Ultra-Turrax T25 shear rate mixer at 7500 rpm for a period of 4–5 min. The product was then centrifuged at 2000 rpm for 10 min to remove any air bubbles trapped in the emulsion.

2.3. In vitro testing for bioadhesive strength

Bioadhesive strength of the lead formulations was determined *in vitro* using a texture analyser XT.RA

Table 1
Formulation of various products prepared for examination as saliva substitutes

[illegible]

Table 2

Formulation of various products prepared for examination as saliva substitutes continued

Formulation	11	12	13	14	15	16	17	18	19	20
Sodium fluoride (mg)	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
Calcium chloride (g)	0.0166	0.0166	0.0166	0.0166	0.0166	0.0166	0.0166	0.0166	0.0166	0.0166
Potassium chloride (g)	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Sodium chloride (g)	0.0844	0.0844	0.0844	0.0844	0.0844	0.0844	0.0844	0.0844	0.0844	0.0844
Magnesium chloride (g)	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058
Potassium phosphate (g)	0.0366	0.0366	0.0366	0.0366	0.0366	0.0366	0.0366	0.0366	0.0366	0.0366
Xylitol (g)	–	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Sorbitol (g)	–	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Zinc sulphate (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Triclosan (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Na lauryl sulphate (g)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Lemon flavour (g)	0.4	0.5	0.5	0.5	1.0	1.0	1.0	1.0	1.0	1.0
Olive oil (g)	–	5.0	10.0	20.0	5.0	10.0	–	–	–	–
Sunflower oil (g)	–	–	–	–	–	–	5.0	10.0	15.0	20.0
Carbopol 974P (g)	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Water (g)	100	100	100	100	100	100	100	100	100	100

(Stable Micro Systems). The apparatus consisted of an upper metal probe (surface area 5.12 cm^2) to which the mucosa or mucus was attached. The sample was placed in a secure position on the lower platform. The probe was lowered at a fixed speed until it came in contact with the sample with a defined force, where it was held for a stated contact time. At the end of this time period, the probe retracted at a defined speed breaking the bioadhesive bond. This procedure was carried out under the adhesive mode. A profile of force versus time was obtained from which the maximum force of detachment F_{max} was measured in mN. The work of adhesion was determined from the area under the curve (N mm). Testing was performed on three different systems, Carbopol 974 1%, product 4 and product 15 using three different model substrates as simulations of the oral mucosa in xerostomic patients, dried porcine gastric mucin (DPGM), fresh porcine oral mucosa (FPOM) and fresh porcine gastric mucus (FPGM).

Dried porcine gastric mucin (20% (w/w)) was prepared by adding the required quantity of powder to distilled water and allowing it to hydrate overnight at 4°C . Fresh porcine oral mucosa was obtained from freshly slaughtered pigs (within 1 h of slaughter). The top layer of tissue was excised from the lower connective tissue layers and cut into suitable sample sizes. The tissue was either used immediately or frozen at -20°C , with greaseproof paper separating individual

samples of tissue. The tissue was defrosted at 4°C as required and used immediately.

Fresh porcine gastric mucus was extracted from recently slaughtered porcine stomach, using a method modified from Mortazavi et al., 1993. Batches of crude mucus were obtained by scraping porcine stomachs received just after slaughter. To the crude mucus was added an equal quantity of an isotonic solution containing PMSF (0.0175% (w/v)), sodium azide (0.02% (w/v)), EDTA (0.186% (w/v)) and sodium chloride (0.9% (w/v)). This mixture was homogenised by blending, with the resulting mixture centrifuged at 3000 g for 1.5 h at 4°C using a temperature-controlled centrifuge (Sorvall, UK). The gel layers were removed from each centrifuge tube, pooled and exhaustively dialysed for 24 h at 4°C in a large volume of water and finally homogenised. If the mucus obtained was not used immediately, it was frozen at -20°C until required and defrosted overnight at 4°C before use.

When using DPGM or FPGM, the probe was covered with a thin layer of each, which was then dried using warm air ($\sim 40^\circ\text{C}$). For FPOM, a thin layer of the tissue was attached to the probe using an adhesive backing layer. The product gels were placed in a glass jar to a depth of 20 mm, with the container anchored to the platform. The probe was brought in contact with the test samples with a force of 0.1 N and held there for a specified period of time and then withdrawn at

a speed of 0.1 mm/s. Five replicates were performed for each sample.

2.4. Rheology

Rheological properties of various systems were evaluated using a Carri-Med rheometer CSL²500 (TA Instruments, UK). All experiments used cone and plate test geometry (angle 4°). The linear viscoelastic region of the systems was first determined by torque sweep.

2.5. Rheological synergism with fresh porcine gastric mucus (FPGM)

Two grams samples of FPGM were mixed with an equal weight of the relevant system, and the pH was adjusted to 6.75 using 10% (w/v) triethanolamine. The final weight of the sample was adjusted to 4.5 g using water. Further mixtures containing 2 g of each system were adjusted to pH 6.75 and made up to 4.5 g using water. A sample containing mucus 2 g and distilled water 2.5 g was prepared also to act as a control. Oscillatory rheometry (triplicate determinations) was carried out on all of the samples listed in Table 3, using a frequency sweep of 0.1–10 Hz at 37°C, with an oscillatory torque of 1350 μ Nm, which was determined to be within the linear viscoelastic range.

2.6. Friction testing of xerostomic products

Friction testing was performed on apparatus that had been constructed in-house. It consisted of a lower fixed plate onto which the test substrate and test substance could be placed, and an upper slider to which different geometries could be attached. The slider moved

along the lower plate at varying speeds and differing distance, creating friction between the two surfaces that could be measured and analysed using in-house developed computer software.

A piece of Perspex[®] 10 cm in length was covered with a soft piece of leather. The leather was used to simulate the oral mucosa (Blanco-Fuente et al., 1996). The upper probe was also covered with the same leather. The sample was loaded onto the 10 cm plate and spread evenly over it. The instrument was put into run mode and the probe moved at a set speed up and down the fixed 10 cm plate for a defined period of time, measured in seconds. All samples were examined at the same speed and distance of travel. The friction was measured in terms of the friction coefficient, μ (force in the direction of motion divided by load applied to the slider). Testing was performed on Carbopol 974P 1% (w/w), product 4 and product 15.

3. Results

3.1. Theory of formulation

Increased incidence of caries is a significant problem associated with xerostomia, as the excretion of minerals in saliva is affected and the pH of the oral cavity is reduced leading to demineralisation of teeth. The functions of the ions present in saliva are to contribute to the osmolarity of saliva and also to its buffering capacity. The buffering capacity of saliva is directly related to its flow, with the difference in resting and stimulated saliva related to the sodium and bicarbonate concentrations. Both sodium and potassium were included in representative formulations listed in Tables 1 and 2, as potassium is the predominant cation in the buffer systems of resting saliva, but sodium predominates in stimulated saliva. The quantities of minerals used in the formulations developed in this project were comparable to those levels of minerals found in natural whole saliva (Edgar, 1992) and are similar in quantity to those in Luborant. Fluoride is an important mineral in caries prevention and therefore is of particular relevance to xerostomic patients. Fluoride is not found in the diet to any large extent and only small quantities are secreted in the saliva. Therefore, fluoride supplementation is required to further improve the patient's chance of maintaining good oral health.

Table 3
Carbopol 974P-based systems examined for rheological synergism

System	1	2	3	4	5	6	7
Porcine gastric mucus (g)	2.0	2.0	2.0	2.0			
Product 4 (g)	2.0				2.0		
Product 15 (g)		2.0				2.0	
Carbopol 974P 1% (g)			2.0				2.0
pH (adjusted to)	6.75	6.75	6.75		6.75	6.75	6.75
Water (g)	4.5	4.5	4.5	4.5	4.5	4.5	4.5