A61K 31/80 (2006.01)  A61K 8/89 (2006.01)
A61K 31/14 (2006.01)  A61P 1/02 (2006.01)
A61K 31/70 (2006.01)  A61Q 11/00 (2006.01)

PCT/UA20 12/000078

22 August 2012 (22.08.2012)

English

7 March 2012 (07.03.2012)

KOZLOVSKYI, Vadim Oleksiiovych [UA/UA]; Gnata Yuri Str., 1/165, Kiev, 03148 (UA);
TOLCHEYEV, Yuriy Zaharovich [UA/UA]; Mayakovska Str., 6a/21, Zugres, Harcizsk, Donetsk region, 86783 (UA).

BLOSHCHYNSKA, Olena Oleksandrivna; Kropivnitskogo Str., 12/1, Kiev, 01004 (UA).

THE USE OF METHYL-SILICIC ACID FOR THE TREATMENT OF PARODONTIUM TISSUES

Disclosed is the use of methyl-silicic acid for the treatment of parodontium tissues based on hydrogen or xerogel of methyl-silicic acid (polymethylsiloxane) for the complex normalisation of the oral cavity microflora in the form of a toothpaste and for reducing the inflammatory and intoxication syndromes. Respectively, a sorbent may be used in combination with bentonite, antibacterial agents and prebiotics.
THE USE OF METHYL-SILICIC ACID FOR THE TREATMENT OF PARODONTIUM TISSUES

Field of the invention

The invention relates to the field of medicine, particularly to the use of methyl-silicic acid forms. This agent relates to the class of sorbents used for the treatment of intoxication syndrome of any aetiology.

Prior art

According to modern teachings, sorbents are agents used in extracorporeal blood purification therapy. The term "extracorporeal blood purification therapy" refers to care which assists in detoxication of a body. Sorption is one of the elements in such a treatment (op cit.: Николаев В.Г., Стрелю В.В., Коробов Н.Ф. и др. Теоретические основы методов трансфузии и методов обезвреживания // Сорбционные методы в медицине: Сборник: Abstracts. Kharkov, 1982, pages 112-114).

Modern sorbents may be divided between two classes of chemical substances which possess different properties, namely:

1) Carbon sorbents of I-IV generations;
2) Sorbents based on natural and synthetic resins, synthetic polymers.
3) Siliceous sorbents comprising organic-silicon aerosils and clays;
4) Natural organic sorbents based on dietary fibers, hydrolysed lignin, chitin, pectins and alginates;
5) Combined sorbents which may consist of two or more types of the above-mentioned sorbents.

All sorbents must, to a certain degree, possess several properties, namely they have to:
1) absorb toxic substances which get into the gastrointestinal tract from outside;
2) absorb toxins which diffuse in the lumen of the intestine from blood;
3) bind toxic substances which release along with digestive juices;
4) absorb toxic metabolites which create directly in the gastrointestinal tract.

However, the use of sorbents in these cases is limited due to the need to take other medicines which may have weakened therapeutic efficacy due to the decrease in their bioavailability. Thus, for example, carbon sorbents are recommended for administration along with other medicines at the maximum possible intervals of time between administrations (op cit: Nikolaev V.G. Peroral Application of Synthetic Activated Charcoal in USSR // Biomat., Art. Cells, Art. Org..- 1990.- Vol.18, N4.- P.555-568.).

Furthermore, there is a number of conditions which, other than intoxication, are accompanied with disorders in other organs and systems.

For example, acute intestinal infections are followed by the development of a condition related to quantitative and qualitative alterations in the intestinal microflora which is classified as dysbiosis.

Intestinal dysbiosis (ID) implies quantitative and qualitative alterations in normal flora of an organ with deterioration of its biological functions and consistent overgrowth of opportunistic enterobacteria, which results from a number of unfavorable factors.

Not coincidentally, the English language publications refer to the term «bacterial overgrowth syndrome», while in German literature the term «bakterielle fehlbesiedlung», meaning erroneous, abnormal colonization of bacteria, is used. Obviously, in such a case it is the specific connotation that matters rather then the term chosen. Thus, this implies changes in flora of the lumen of the small intestine due to abnormal colonization of bacteria, as well as drastic decrease in the number of normal microflora of the genus Bifidobacterium, Escherichia Coli and simultaneous increase in the contents of colibacillus with weak enzymatic properties, lactose-negative enterobacteria, Candida genus fungi, etc. in the colon.

However, similar changes occur not only in the intestine, but also in other body cavities where natural microorganisms are present, particularly in the oral cavity, and their disbalance is a developing factor for parodontium diseases, for instance periodontitis and paradontosis.
The issue of the treatment and prevention of parodontium diseases is among the key challenges in modern dentistry. The incidence of this pathology is constantly growing. Based on the results of a study performed by the WHO in 35 countries among patients aged 31 to 44 years, in 7 countries a very high incidence of parodontium diseases was detected (over 75%), in 13 countries it was classified as high (40 to 75%), and in 15 countries - as moderate (under 40%).

Microorganisms that are localized directly on the surface of the enamel, as well as in pockets between the teeth and the gums are currently believed to cause pathological conditions in parodontium, as well as to be able to cause a systemic action.

An inflammatory process localized in parodontium tissues is most often caused by various microbial agents for which dental plaque serves as a primary source. The following species of microorganisms are responsible for severe clinical picture of paradontosis: Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia, Treponema denticola.

Published scientific sources teach that these microorganisms are distinguished as being the most aggressive and having the highest ability to penetrate into the parodontium tissues due to the release of lytic enzymes. These microorganisms also participate in the formation of an immune response of the body to their penetration into the parodontium tissues, causing development of an autoimmune inflammation or an immunodeficiency condition which lowers the efficiency of treatment (cf. Курякина Н.В., Кутепова Т.Ф. Заболевания пародонта. М., «Медицинская книга», 2003. - 158 с. (Kuryakina N.V., Kutepova T.F. Parodontium diseases. Moscow. Meditsynskaya kniga, 2003, page 158); Talbert J., Elter J., Jared H.L., Offenbacher S. et al. The effect of periodontal therapy on TNF-alpha, IL-6 and metabolic control in type 2 diabetics. // J Dent Hyg., 2006 Spring; 80(2) - p.7)/

An increase in the production of anti-inflammatory mediator cytokines (IL-1, IL-6, IL-8 and others) by tissular macrophages of the lymphoid tissue is accompanied by the development of multiple local and systemic effects which ultimately result in disruption of microcirculation in the parodontium tissue, disintegration of collagen of peridental ligament and resorption of bone tissues in dental processes due to changes in the degree of differentiation of osteoclast precursor cells.

The existing methods of treatment of paradontosis are, first of all, linked to the local (and sometimes to systemic) use of antibacterial and antiseptic preparations and reparants.
Particularly, there is a method of treatment of parodontitis (see the manual Ваер Г.М., Лемецкая Т. И. "ХВОРОБИ ПАРОДОНТУ. КліНіКа, фізіоТВКа Та JiіKyBaHHa", М.: BYHМУ., 1996 р./Barer G.M., Lemetskaya T.I. Parodontium diseases. Clinical picture, diagnostics and treatment. Moscow. VUNMC, 1996), which provides for prior treatment to include treatment of tooth decay and its complications, changing dental sealants with hanging edges, removing contact points. Then dental deposits are removed, with the removal of tooth plaque, followed with thorough sanation of oral cavity, rinsing pockets with various antiseptic solutions (chlorhexidine, trichopol, trypsin, chemotryptsin, etc.), curettage of parodontium pockets, curettage according to the method of N.I. Znamensky.

If certain teeth are missing in a patient, an orthopedic treatment is performed. Surgery is followed by an antiseptic treatment of the gums, administration of polyvitamins, salicylates, antihistamines and physiotherapy depending on the indications.

Disadvantages of this method include complexity of the full course of treatment, a long-term intake of difference medicines which may cause side effects, for example, dysbacteriosis, traumatic character of surgical procedures. Such treatment often requires to be followed by physiotherapy due to present inflammatory processes resulting from surgery.

For example, RU Patents no 2089243 (publication date 10.09.1997) and no. 2147868 (publication date 27.04.2000) disclose the use of traumatic instrumental methods for the treatment of parodontium, primarily directed towards the removal of dental deposits, and the use of physiotherapy methods for the improvement of blood circulation in dental tissues. However, such methods can not totally resolve the problem of treatment of parodontosis and parodontium since they do not sufficiently target the main cause of this disease, namely the content of microorganisms in the oral cavity.

Therefore, on one hand, constant attempts have been made to normalize the content of dental and oral cavity microflora, and, on the other hand, to provide remineralisation of tissues, primarily with calcium. Particularly, RU Patent 2271769, A61C 5/00, A61K 6/033, A61K 35/32, 2004 p. discloses a method comprising removal of undergom tooth deposits, removal of traumatogenic occlusion, curettage, surgical treatment, drug therapy, local refill with calcium with the use of the preparation Hydroxiapol.
It was unexpectedly found that the local use of sorbents for this purpose can reduce manifestations of intoxication, on one hand, and normalize the qualitative and quantitative properties of microflora, on the other hand.

It is known that the traditional use of sorbents can improve the condition of such patients, but it is not always the case. Scientific literature refers to ulcerative erosive disease of mucous membranes caused by longtime use of activated carbon as an active sorbent or its application in large doses (op cit: Mizutani T, Naito H, Oohashi N. Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning.// Hum Exp Toxicol. 1991 Sep;10(5):385-6).

Furthermore, the use of activated carbon is related to quite unpleasant organoleptic properties, while it is also poorly wettable by saliva.

For example, international application WO/2010/124329 discloses a method for the preparation of an aqueous suspension of activated carbon with the use of surfactants for wetting carbon particles, while US patent application no. 20090180936 US (publication date) discloses a method for improving the efficiency of carbon by hydroxypropylmethylcellulose and different drugs immobilized on carbon.

However, the use of carbon does not allow to fully resolve the problem of detoxication in case of different pathologies in dentistry.

There is also a known method involving the use of silica dioxide which possesses strong sorption and low-abrasive activity in toothpaste compositions (USSR patent no 623555, A 61 K 7/28, 1978; RU patent no 2012329, A 61 K 7/16, 1996.; US Patent no 5192529, A 61 K 7/16, 1993.: US patent no. 5300283, A 61 K 7/18, 1994.; US patent no. 4923648, A 61 K 7/16, 1990, GB application no. 2272640, A 61 K 7/16, 1994, RU no. 2112502, publication date 1998.06.10.), as well as other materials having sorption activity, for example carboxymethylcellulose (RU patent no. 2014829, A 61 K 7/16, 1996). However, neither the use of silica dioxide itself, nor its combination with antiseptics is efficient in the prevention, and the more so in the treatment of parodontosis.

Therefore, new chemical compounds are being researched which, on one hand, may be used as sorbents and, on the other hand, would restore the oral microflora.

It was unexpectedly found that hydrogel and xerogel of methyl-silicic acid known under the chemical name polymethylsiloxane have these properties.

General sources teach that hydrogel of methyl-silicic acid can bind microorganisms (for example, UA patent no 82774 (published on 12.05.2008, Bulletin
no. 9) and medium molecular weight substances. However, there is practically no teaching over the use of hydrogel of methyl-silicic acid in the treatment of parodontium diseases accompanied by the intoxication syndrome.

Summary of the invention

The problem solved by the invention lies in the local use of hydrogel or xerogel of methyl-silicic acid for the treatment of disorders in the content and balance of oral cavity microflora caused by various factors and for reducing manifestations of the inflammatory and intoxication syndromes accompanying parodontium diseases.

This problem is solved by the invention according to which hydrogel or xerogel of methyl-silicic acid is used locally for the treatment of oral cavity disorders accompanied by the inflammatory and intoxication syndromes.

Thus, the use of hydrogel and xerogel of methyl-silicic acid can provide complex restoration of the normal state of the oral cavity microflora and result in reducing manifestations of the local and systemic intoxication syndrome.

The first characterizing feature lies in that hydrogel or xerogel of methyl-silicic acid is used locally as a component in toothpastes. Such an application is suitable for the treatment of those patients suffering from parodontosis, which have significant manifestations of the intoxication syndrome, especially those accompanying oral infections.

The second characterizing feature lies in that hydrogel or xerogel of methyl-silicic acid additionally comprises bentonite. This composition is the most suitable for continuous prevention and treatment of patients, especially children and elderlies, as well as patients undergoing treatment with antibiotics.

The third characterizing feature lies in that hydrogel or xerogel of methyl-silicic acid additionally comprises an antibacterial agent optionally selected from the group consisting of thymol, chlorhexidine, metronidazole, benzalconium chloride.

The fourth characterizing feature lies in that hydrogel or xerogel of methyl-silicic acid additionally comprises a prebiotic optionally selected from the group consisting of inulin, lactulose, beta-glucan, etc.

Detailed description of the invention

The invention is further disclosed through the description of a method of use of hydrogel or xerogel of methyl-silicic acid for the treatment of oral cavity diseases, and
particularly with reference to experimental forms and experiments performed on laboratory models, as well as to the obtained results as compared to the effect of the traditional preparations, and with reference to the use guidelines.

1) Method of use.

Hydrogel or xerogel of methyl-silicic acid are obtained with the use of well-known techniques and then applied on teeth with a tooth brush.

A person skilled in the art will appreciate that calculation of the respective concentrations are made based on well-known methods.

Experimental forms as toothpastes were prepared by mixing hydrogel of methyl-silicic acid and solutions of xylitol, sorbitol, monofluorophosphate, bentonite, fillers and structure-forming substances, such as, for example, sodium or calcium alginate, guar gum, inulin, with the addition of preservatives and flavouring agents, such as, for example, sodium saccharinate, cyclamate, thaumatin, etc. The most efficient components ratio for the preparation of such a toothpaste was 10% - 50% hydrogel of methyl-silicic acid and 90%-50% other structure-forming agents. Afterwards, the teeth, gums and the oral cavity were treated with such paste-like preparations.

Example 1. Preparation of a paste-like product with different ratios of hydrogel of methyl-silicic acid and water solution of polysaccharide.

30 g 3% water solution of lactulose are added to 70 g of hydrogel of methyl-silicic acid, and then traditional components of toothpastes are added to the mixture in the ratio 1:1.

Example 2. Preparation of a paste-like product with different ratios of hydrogel of methyl-silicic acid and water solution of polysaccharide.

30 g 5% water solution of inulin are added to 70 g of hydrogel of methyl-silicic acid, and then traditional components of toothpastes are added to the mixture in the ratio 1:1.

Persons skilled in the art will appreciate that the preparation of ordinary toothpastes with a specific content of substances and, if necessary, well-known additives is based on standard techniques.

2) Practical embodiments of the invention

The efficiency of use of hydrogel and xerogel of methyl-silicic acid was experimentally assessed according to the officially recommended method (The results of treatment were estimated based on the data of clinical study in dynamics: examination, determining the depth of parodontium pockets, Fedorov-Volodkina
hygienic index (HI), RMA index, Schiller-Pisarev test, bleeding index (BI), determining functional capillary resistance by V.I. Kulazhenko (FCR)).

The obtained data were processed statistically. The symbol (*) in the table following digital values indicates that statistical discrepancy is $p < 0.05$ as compared to the control (ordinary hygienic toothpastes).

Comparative therapeutic efficiency data

(Table 1)

<table>
<thead>
<tr>
<th>Index name</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>$P_{1-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without treatment (1)</td>
<td>Polymethylsiloxane hydrate 70%/30% 1% water solution of lactulose (2)</td>
</tr>
<tr>
<td>HI</td>
<td>2,25±0,10</td>
<td>1,55±0,15</td>
<td>1,25±0,12</td>
</tr>
<tr>
<td>RMA</td>
<td>22,5±4,40</td>
<td>14,28±1,10</td>
<td>10,5±1,10</td>
</tr>
<tr>
<td>BI</td>
<td>4,95±1,10</td>
<td>2,32±0,80</td>
<td>1,25±0,12</td>
</tr>
<tr>
<td>FCR</td>
<td>18,75±1,15</td>
<td>22,25±0,14</td>
<td>42,25±4,10</td>
</tr>
</tbody>
</table>

Comparative data for the effect of the preparations on the state of microcenosis

(Table 2)

<table>
<thead>
<tr>
<th>Microflora</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>$P_{1-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Without treatment (1)</td>
<td>Polymethylsiloxane hydrate 70%/30% 1% water solution of lactulose (2)</td>
</tr>
<tr>
<td>Lactobacteria</td>
<td>$10^5$-$10^7$</td>
<td>$10^7$-$10^8$</td>
<td>$10^8$-$10^9$</td>
</tr>
<tr>
<td>Bifidobacteria</td>
<td>$10^4$-$10^5$</td>
<td>$10^5$-$10^7$</td>
<td>$10^7$-$10^8$</td>
</tr>
<tr>
<td>Treponema denticola</td>
<td>$10^4$-$10^5$</td>
<td>$10^4$-$10^5$</td>
<td>$10^1$</td>
</tr>
</tbody>
</table>

The study of the data provided in Tables 1 and 2 shows that polymethylsiloxane hydrate is capable of reducing manifestations of dysbiotic changes in the oral cavity and improving the condition of the parodontium tissues.
The use recommendations are based on the established eubiotic and anti-inflammatory properties. Therefore, hydrogel or xerogel of methyl-silicic acid should be used for the prevention of the development of dysbacteriosis in the oral cavity and for the prevention and treatment of parodontium diseases and their different complications, especially those related to intoxication.

Hydrogel or xerogel of methyl-silicic acid is commercially available and is approved for the use in the cosmetic and food industries. This justifies the expansion of its use to the field of medicine, particularly to the prevention and treatment of patients with parodontium diseases.
1. The use of methyl-silicic acid as an agent for the treatment of parodontium tissues.
2. The use according to claim 1, wherein methyl-silicic acid is in the form of xerogel.
3. The use according to claim 1, wherein methyl-silicic acid is in the form of hydrogel.
4. The use according to claim 3, wherein methyl-silicic acid is a component in toothpastes.
5. The use according to claim 4, wherein methyl-silicic acid is based on bentonite.
6. The use according to claim 4, wherein methyl-silicic acid is used along with an antibacterial agent preferably selected from the group consisting of thymol, benzalconium chloride, chlorhexidine.
7. The use according to claim 4, wherein methyl-silicic acid is used along with a prebiotic preferably selected from the group consisting of inulin, lactulose, beta-glucan.
8. The use according to claim 4, wherein methyl-silicic acid is used along with at least one metabolic agent preferably selected from the group consisting of adenosine, adenosinetriphosphate, guanosine, barrenwort extract, red mold extract.
INTERNATIONAL SEARCH REPORT

PCT/UA 2012/000078

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/80 (2006.01) A61K 8/89 (2006.01)
A61K 31/14 (2006.01) A61P 1/02 (2006.01)
A61K 31/70 (2006.01) A61Q 11/00 (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)

A61K 8/89, 31/74, 31/80, 31/14, 31/70, 31/7052, 36/00, 36/06, A61P 1/02, A61Q 11/00

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>UA 18061 A (YAROVA SVETLANA PAVLOVNA et al.) 3 1.10. 1997, claim, abstract</td>
<td>1, 3</td>
</tr>
<tr>
<td>Y</td>
<td>UA 43574 U (YAROVA SVETLANA PAVLOVNA et al.) 25.08.2009, claim, abstract</td>
<td>2, 4-8</td>
</tr>
<tr>
<td>Y</td>
<td>WO 2006/360565 A1 (TOLCHEEV YURI et al.) 27.03.2008, abstract, p. 3, line 16, examples 41, 40</td>
<td>2, 6</td>
</tr>
<tr>
<td>Y</td>
<td>KZ 22885 A4 (SAKIPOVA ZURIYADDA BEKTEMIROVNA) 15.09.2010, claims, abstract, last paragraph after table 1</td>
<td>4-8</td>
</tr>
<tr>
<td>Y</td>
<td>RU 2355420 C2 (KLOPOTENKO LEONID LEONIDOVICH) 20.05.2009, abstract, p. 6, line 1-2</td>
<td>7</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "X" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document 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

Date of the actual completion of the international search
19 November 2012 (19. 11.20 12)

Date of mailing of the international search report
13 December 2012 (13. 12.20 12)

Name and mailing address of the ISA/ FIPS
Russia, 123995, Moscow, G-59, GSP-5, Berezkovskaya nab., 30-1
Facsimile No. +7 (499) 243-33-37

Authorized officer
K. Savchenko
Telephone No. (495) 531-64-81

Form PCT/ISA/210 (second sheet) (July 2009)
### INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/UA 2012/000078

**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>RU 2316242 C2 (DZE PROKTER END GEMBL KOMPANI) 10.02.2008, p. 19, lines 37-38, p. 14, line 38, claim 9</td>
<td>6, 7</td>
</tr>
<tr>
<td>Y</td>
<td>GB 1.422642 A (PAPIERWERKE WALDASCHAFFENBURG) 28.01.1976, abstract</td>
<td>8</td>
</tr>
<tr>
<td>Y</td>
<td>US 4948783 A (KABUSHIKI KAISYS ADVANCE KAIHATSU KENKYUJO.) 14.08.1990, claims, col. 2, line 67, col. 3, line 1, col. 3, line 11-17</td>
<td>8</td>
</tr>
<tr>
<td>Y</td>
<td>JP 2001-089386 A (KOBAYASHI PHARMACEUT CO) 03.04.2001, abstract</td>
<td>8</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (July 2009)